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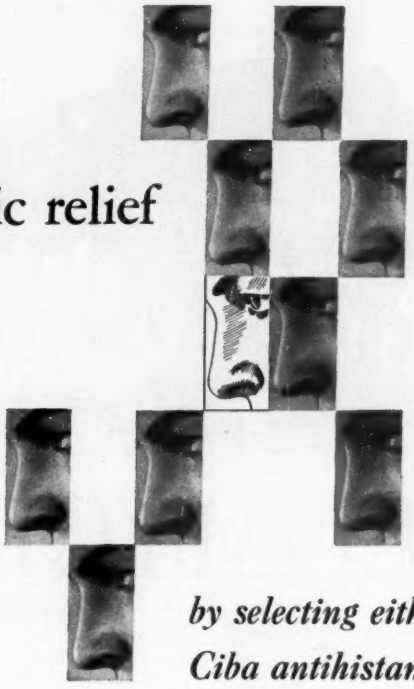

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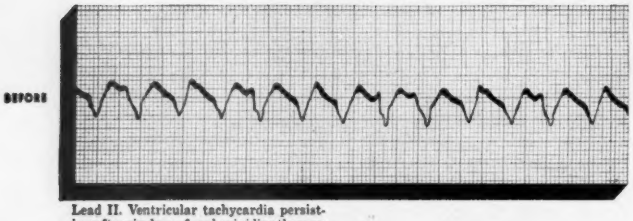
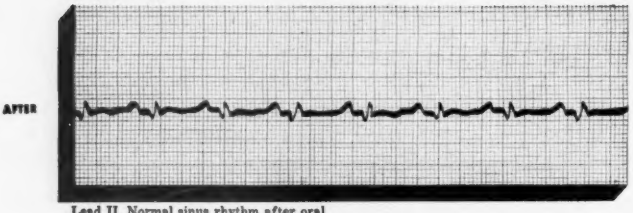


Lead II. Ventricular tachycardia persisting after six days of oral quinidine therapy (8 Gm. per day).



Lead II. Normal sinus rhythm after oral Pronestyl therapy.

Effective in some patients with ventricular tachycardia who failed to respond to quinidine

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When is it indicated?

In conscious patients, for the treatment of ventricular arrhythmias.

During anesthesia, to correct cardiac arrhythmias.

What are its advantages in ventricular arrhythmias?

As compared with quinidine: Unlike quinidine, no important toxic symptoms have been reported following the use of Pronestyl orally. In therapeutic dosage, Pronestyl orally does not produce the nausea, vomiting, and diarrhea often caused by quinidine. At high oral dosage, these symptoms may appear.

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As compared with procaine: For arrhythmias, procaine is used only in anesthetized patients because its dose in unanesthetized patients is too toxic for clinical use. Pronestyl can be used in conscious and anesthetized patients.

Intravenously, Pronestyl is much less toxic than procaine. In the recommended intravenous dosage, Pronestyl does not cause the central nervous system stimulation typical of procaine in conscious patients.

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Procaine is not used orally because of its instability in the organism; Pronestyl can be used orally and intravenously.

What are its side effects?

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What is the dosage?

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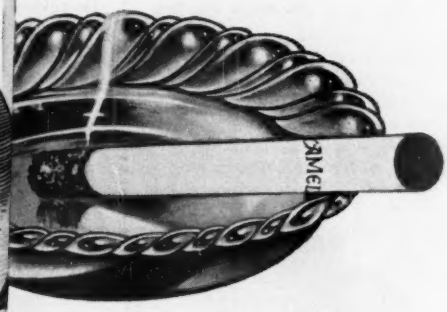

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Volume 244 MARCH 1, 1951 Number 9

KHELLIN IN THE TREATMENT OF ANGINA PECTORIS*

HAROLD L. OSHER, M.D.,† KERMIT H. KATZ, M.D.,‡ AND DONALD J. WAGNER, M.D.†

BOSTON

KHELLIN§ is a pure crystalline derivative of *Ammi visnaga*, a plant that grows wild in the eastern Mediterranean countries, and that is known in Arabic as "khella." The medicinal properties of this plant have apparently been known since ancient times, and a decoction of its seeds has been used by the native populations for many centuries as an antispasmodic for the treatment of renal colic. However, the first recorded pharmacological study of *Ammi visnaga* is that of Mustapha,[1] who in 1879 isolated the chief active principle, khellin, in impure form. Since that time, an extensive series of investigations[2-17] has clearly demonstrated the chemical structure and pharmacological properties of khellin as well as of two other crystalline derivatives of the plant.

Chemically, khellin is a dimethoxy-methyl-furanochromone with the formula $C_{14}H_{12}O_4$.[7] The findings of Samaan,[10] who suggested the name "visammin" for khellin, indicate that it relaxes visceral smooth muscle by a direct effect on the muscle fiber; Anrep and others[13-16] have confirmed and extended these observations, pointing out that khellin has an exceptionally potent and prolonged coronary vasodilator effect. Experiments of Anrep's group, using the dog heart-lung preparation,[13] have been reported as showing that khellin concentrations of approximately 1:200,000 produce a threefold increase in coronary sinus outflow, and that the coronary vasodilator action of khellin, while less than that of amyl nitrite, is at least four times as great as that of aminophyllin.[14, 16] Absorption of khellin is rapid, a maximum blood concentration being reached within thirty to sixty minutes after oral administration, and within five to ten minutes after intramuscular injection. It is distributed almost uniformly through all body tissues, and its destruction and excretion proceed so slowly that repeated doses have a cumulative effect.[16, 17] Systemic blood pressure is not altered by therapeutic concentrations of khellin, apparently because the systemic arteries are much less susceptible to its action than are the coronary arteries.[14, 16] No harmful effects on the myocardium, kidney or other organs have been observed, nor has development of tolerance to the drug been noted even after prolonged administration.[14]

Visnagin, the second crystalline derivative of *Ammi visnaga*, differs chemically from khellin in having a single methoxy group, and pharmacologically in being somewhat less potent in relaxing smooth muscle. It is present in such small amounts as to be of no practical importance.[8, 14, 16] The third crystalline substance, an oxyglucoside of visnagin known as khellol-glucoside or khellinin, is pharmacologically inactive, is not absorbed from the gastrointestinal tract, and is not converted in the body to khellin.[9, 16, 17]

Anrep and co-workers have recently reported their observations on the treatment of angina pectoris with khellin; of 250 patients treated, 225 (90 per cent) were considered to be improved — 140 (56 per cent) markedly and 85 (34 per cent) moderately.[14] Ayad, reporting on the treatment of 23 patients, stated that the anginal attacks disappeared completely in 14, were markedly improved in 5, and were unchanged in the remaining 4 patients.[18] Dewar and Grimson demonstrated that well tolerated single doses of khellin, given shortly before standard exercise, frequently prevented or diminished anginal pain and associated electrocardiographic changes that otherwise occurred in certain patients with angina of effort.[19] Rosenman and his associates, in a controlled study of 14 patients, concluded that marked improvement occurred in 11, moderate improvement in 1 and little or no improvement in 2; of 8 additional patients in whom careful control was not possible, 6 were thought to be markedly improved and 2 moderately improved.[20]

In a preliminary report of the present study, we stated that 16 of 19 patients exhibited evidence of

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§The preparation of khellin (Eskel) used in this study was supplied by the Smith, Kline and French Laboratories of Philadelphia, Pennsylvania. It contains a mixture of 70 to 80 per cent khellin and 20 to 30 per cent visnagin, and its activity is expressed in terms of pure crystalline khellin.

improvement with khellin therapy; improvement was considered marked in 5 patients, moderate in 10 and slight in 1.[21]

Materials and Methods

The present study was designed to evaluate therapy in angina pectoris with khellin by controlled objective and subjective methods. Patients with well established angina pectoris were selected from the cardiac clinic of the Boston City Hospital.

Preliminary studies on each patient included a medical history, physical examination, blood counts, urinalysis, Hinton test, electrocardiogram, x-ray examination of the heart and, in some cases, cardiac fluoroscopy. Since many of the patients had been followed in the clinic for months or years and had been treated with a variety of medications, some knowledge of their condition and response to therapy was available at the outset. In addition, the severity of the disease was estimated in each patient during a control period of observation by noting the frequency of anginal attacks and the number of nitroglycerin tablets required, and by repeated measurements of exercise tolerance, using the two-step test under standard conditions, essentially as described by Riseman and Stern.[22] Exercise was continued at a comfortable, constant rate until pain became sufficiently well developed to force the patient to stop. After a consistent base line had been established, therapy was begun and the aforementioned observations were repeated at intervals of four to fourteen days. Resting electrocardiograms were taken at least once during the period of therapy in most patients, and in 9 cases comparison of the electrocardiographic changes induced by standard exercise before and during treatment was made. Placebos, identical in physical characteristics with khellin, were given either at the outset or after a period of khellin therapy, or both. Khellin was given in the form of sugar-coated tablets containing the equivalent of 40 mg. of the crystalline substance; these were taken orally an average of 4 times daily, after meals and before retiring.

Carefully controlled observations were made on 32 patients over periods ranging from three to ten and a half months. There were 26 men and 6 women, ranging in age from 49 to 81 years; two patients were Negroes and the others white. In addition to coronary-artery disease, hypertension was present in 21 patients, aortic stenosis and insufficiency in 2, mitral stenosis in 1 and diabetes mellitus in 2. The Hinton test was negative in all patients. Thirteen patients had a definite history of one or more myocardial infarctions, and 3 additional patients showed electrocardiographic evidence of old infarctions.

The degree of improvement was classified as marked when anginal pains became infrequent and mild, and when the exercise tolerance either doubled or was apparently prevented from doubling by fatigue, dyspnea or intermittent claudication rather than by anginal pain. Patients were considered moderately improved when nitroglycerin requirements were at least halved (reflecting a corresponding decrease in pains) and exercise tolerance was increased at least one third unless limited by the nonanginal factors noted above. Definite subjectively and objectively measurable improvement of lesser degree was classified as slight.

Results

Of the 32 patients, 26 experienced a decrease in frequency and severity of anginal pains, a drop in nitroglycerin requirements and an increase in exercise tolerance. This improvement was considered marked in 11 patients, moderate in 11 and slight in 4; the remaining 6 showed no improvement. Detailed observations on the entire group are summarized in the accompanying table (Table 1).

Five additional patients, also treated with khellin, were excluded from the above group either because they were unable to perform the exercise-tolerance test or because they could not be studied for a sufficient period of time. These patients, afflicted with severe and at times intractable angina, all experienced moderate or marked reduction in frequency and severity of pains and in nitroglycerin requirements.

Placebos were given to 21 patients at the outset in order to evaluate possible psychic factors. A few patients claimed increased well-being or slight diminution of pain, but in only one patient (Patient 27) was there actual decrease in the reported frequency of pain and of nitroglycerin requirement; none of the patients demonstrated a significant increase in exercise tolerance. Seventeen of the 21 thereafter improved when khellin was given; the patient who had claimed benefit from the placebo was one of the four who failed to improve with khellin. Fourteen of the 17 patients who improved were again given placebos; 10 relapsed promptly to their pretreatment status, and the remaining 4 patients experienced delayed and less complete relapses. Eleven patients were given khellin initially, and the 9 who improved were subsequently given placebos; prompt, complete relapses occurred in 6, delayed or incomplete relapses in 2 and no relapse in 1. Several patients experienced repeated relapses when placebos were given a second or third time. There were four patients who did not relapse after a prolonged period of khellin therapy; the significance of this observation will be discussed later.

Although patients were observed for periods varying from three to ten and a half months, the duration of khellin therapy ranged from seven weeks to nine months; the average duration of treatment for the 32 patients exceeded four months. Effective daily khellin dosage ranged from 120 to

TABLE 1.

Case No.	Age	Sex	Diagnosis	Duration of Angina Pectoris	Before Treatment			After Treatment			Duration of Treatment	Khellin Dosage	Subjective Improvement	Objective Improvement
					Two-step test trips	time	Nitroglycerin tablets per week	Two-step test trips	time	Nitroglycerin tablets per week				
	yr.			yr.		min.			min.		mo.	mg.		
1	57	M	Arteriosclerotic heart disease	1½	20	1½	14–21	54*	0–3	0–1	2½	160	Marked	Marked
2	57	M	Arteriosclerotic heart disease, old myocardial infarction, hypertension, diabetes mellitus	2½	53	4½	3–5	77†	6	0–1	5	120	Marked	Marked
3	63	M	Arteriosclerotic heart disease, old myocardial infarction	2½	26	2½	2–4	55	5	0–2	8	120	Marked	Marked
4	55	M	Arteriosclerotic heart disease	2½	17	1½	3–4	50*	3½	0	6	120	Marked	Marked
5	53	M	Arteriosclerotic heart disease, old myocardial infarction, hypertension	7	28	2	3–6	62	4	0–1	9	120	Marked	Marked
6	74	M	Arteriosclerotic heart disease, old myocardial infarction, hypertension	7	16	3	5–10	21†	3½	0–1	5	160	Marked	Marked
7	71	F	Arteriosclerotic heart disease, hypertension	10	17	2	3–4	29*	2¾	0	5	120	Marked	Marked
8	55	F	Arteriosclerotic heart disease, old myocardial infarction, diabetes mellitus	4	20	2½	14–23	43†	5	1–5	4	160	Marked	Marked
9	81	M	Arteriosclerotic heart disease, old myocardial infarction, hypertension	3	19	2	15–30	22†	2	1–4	3	120	Marked	Marked
10	67	M	Arteriosclerotic heart disease, hypertension	1	28	2½	2–3	50†	4½	0–1	3	160	Marked	Marked
11	69	F	Arteriosclerotic heart disease, aortic stenosis and insufficiency, hypertension	½	28	4	8–16	35†	5	2–4	3	160	Marked	Marked
12	52	M	Arteriosclerotic heart disease	1½	23	1½	20–30	33	2½	1–7	2½	160	Marked	Moderate
13	52	M	Arteriosclerotic heart disease, old myocardial infarction, hypertension	1	48	3½	3–10	55†	4	0–2	3	160	Moderate	Moderate
14	57	F	Arteriosclerotic heart disease, old myocardial infarction, hypertension	1½	30	2½	2–5	41	3	0–1	9	120	Moderate	Moderate
15	50	M	Arteriosclerotic heart disease, old myocardial infarction, hypertension	4	43	4	5–9	62	5	0–2	5	200	Moderate	Moderate
16	53	M	Arteriosclerotic heart disease	2	45	3½	15–25	64	5	4–8	7	160	Moderate	Moderate
17	56	M	Arteriosclerotic heart disease, hypertension	2	34	2¾	6–12	52	4	0–3	3	160	Moderate	Moderate
18	61	M	Arteriosclerotic heart disease, old myocardial infarction, hypertension	4	50	4	None	65*	5¼	None	4	200	Moderate	Moderate
19	70	M	Arteriosclerotic heart disease	1	30	2	12–20	35*	2¼	3–6	2	160	Moderate	Moderate
20	65	M	Arteriosclerotic heart disease, old myocardial infarction, hypertension	4	41	3¼	0–2	55†	4	0	5	200	Moderate	Moderate
21	58	M	Arteriosclerotic heart disease, old myocardial infarction, hypertension	3	28	2¾	3–9	35†	2¾	0–3	3	160	Moderate	Moderate
22	49	M	Arteriosclerotic heart disease, old myocardial infarction, hypertension	3	23	2	20–30	40	3	7–20	6	160	Moderate	Moderate
23	64	M	Arteriosclerotic heart disease	1	26	2	10–18	35	3	6–12	5	240	Slight	Slight
24	63	F	Arteriosclerotic heart disease, hypertension	13	18	2½	None	22	3½	None	2	160	Moderate	Slight
25	64	M	Arteriosclerotic heart disease, hypertension	1	30	2	1–3	35†	2½	0–1	3	240	Slight	Moderate
26	50	M	Arteriosclerotic heart disease, old myocardial infarction, hypertension	7	25	2	None	30	2½	None	4	240	Slight	Slight
27	54	M	Arteriosclerotic heart disease, old myocardial infarction	3	19	1½	14–20	22	1½	7–10	4	160	Slight	None
28	64	F	Arteriosclerotic heart disease, aortic stenosis and insufficiency, hypertension	6	27	2	4–8	25	2	4–8	3	80	None	None
29	52	M	Arteriosclerotic heart disease, rheumatic heart disease	1	48	4	1–2	48	4	1–2	6	120	None	None
30	59	M	Arteriosclerotic heart disease, hypertension	2	53	3½	1–4	55	3½	1–4	2	200	None	None
31	49	M	Arteriosclerotic heart disease, old myocardial infarction, hypertension	2	18	1¾	1–2	19	1¾	1–2	3	160	None	None
32	49	M	Arteriosclerotic heart disease	3	38	2¾	1–4	38	2¾	1–4	1½	200	None	None

*No pain; exercise limited by fatigue, dyspnea or intermittent claudication.

†Pain present, but mild; exercise limited by fatigue, dyspnea or intermittent claudication.

240 mg., with an average of 160 mg. Of the 26 patients who improved with khellin therapy, the dose required for optimum benefit was 120 mg. in seven patients, 160 mg. in 13, 200 mg. in three and 240 mg. in three. Of the six patients who did not improve, one could tolerate only 80 mg., another 120 mg. and a third 200 mg.; two were not given doses exceeding 160 mg., and one was not given a dose exceeding 200 mg. In all but the latter three patients, the daily dose was gradually raised by 40-mg. increments to a level which effected either satisfactory improvement or a toxic reaction. Frequently the dose required for maintenance of improvement was less than that needed to initiate it, although no attempt was made to determine the minimum effective maintenance dose in each case. Improvement began within one or two weeks after an effective dose was given. No correlation was noted between the severity of angina and the dose required.

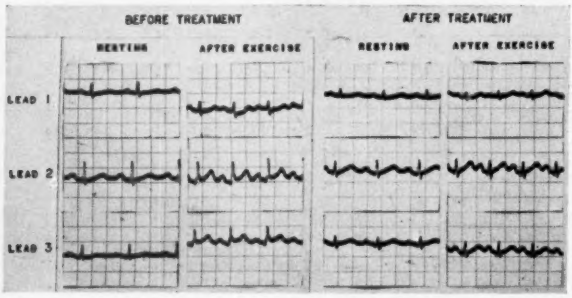

FIGURE 1. *Resting Electrocardiograms Are Identical before and after Treatment. Before Treatment, Standard Exercise Induced a Less Common Type of Electrocardiographic Response, with Depression of the ST segment in Lead 1 and Reciprocal Elevation of the ST Segments in Leads 2 and 3 — the Pattern of Ischemia of the Posterior Myocardium. After Khellin Therapy, These Electrocardiographic Changes Could Not Be Reproduced by the Same Standard Exercise (Case 19).*

Toxic reactions to therapeutic doses of khellin (gastric irritation and insomnia) were generally not severe. Nausea and vomiting limited the daily dose to 80 mg. in one patient and 120 mg. in another; khellin therapy could not be evaluated in a third patient because of inability to tolerate the initial daily dose of 120 mg. Transient, mild nausea and vomiting occurred in three patients during the first few days of treatment but thereafter subsided and did not recur in spite of continuation of the same dose. Mild anorexia was noted in two cases but was not sufficiently troublesome to interfere with treatment. One patient complained of vague epigastric discomfort, while another experienced troublesome insomnia unless his maintenance dose was taken early in the day. Six additional patients, who had improved with small or moderate doses, noted similar untoward reactions when higher doses were administered in an effort to induce further improvement. Miscellaneous complaints, including mild dizziness and constipation, at first thought to be related to khellin therapy, were subsequently found to occur in the same patients while receiving a placebo or no treatment at all. In order to lessen gastric irritation, khellin was given in divided doses of 40 to 80 mg. following meals; an additional dose taken at bedtime by several patients was well tolerated with the single exception noted previously. No significant alterations in blood pressure were observed during the period of khellin treatment. The only death in the series, due to acute myocardial infarction, was that of Patient 9 while he was receiving khellin. There were no adverse reactions to the exercise tolerance test.

The resting electrocardiogram was not altered by khellin treatment. In nine patients electrocardiographic changes induced by standard exercise before and during khellin therapy were compared; khellin therapy had no effect on the electrocardiographic changes in five patients, diminished them in two and eliminated them in two others (Figures 1 and 2).

COMMENT

The difficulty of evaluating drug therapy in angina pectoris is well known, and results largely from irregular and unpredictable variations in the severity of the disease. Spontaneous remissions often occur; these may be attributed to decreased activity or emotional stress, warm weather, avoidance of overeating and other precipitating causes, improvement in collateral circulation and, probably, other obscure factors. The problem is further compli-

cated by the psychologic effects of new medication and sympathetic medical attention.

As noted above, our knowledge of the previous condition and response to therapy of many patients, supplemented by the information obtained during the control period of observation, provided a valuable basis for comparison. The general level of physical activity of each patient remained approximately constant throughout the period of study, except in those cases where an increase was associated with beneficial effects of treatment. The time of treatment was such that in many patients improvement occurred during the cold winter months, when exacerbation of symptoms was expected on the basis of previous experience. The rapid action of khellin, by making evaluation of its effects possible within a short time, minimized the opportunity for improvement due to extraneous factors. The use of placebos, particularly when given at the outset, permitted estimation of the influence of psychic and other factors unrelated to khellin therapy. Recording of the exact number of anginal pains experienced and nitroglycerin tablets required with a known level of activity served not only as an index of the patient's condition, but also as a check on his subjective estimate of his own condition. The use of standardized exercise tolerance tests during all phases of observation, particularly when combined with recording of electrocardiographic changes, provided an objective means of assessing khellin therapy. Although each of these methods of evaluation, including the so-called objective ones, may be subject to certain inherent shortcomings and inaccuracies, the closely correlated results obtained by essentially independent methods, together with the striking degree of improvement frequently observed, appears to constitute reliable evidence of the efficacy of khellin therapy.

It is noteworthy that in over two thirds of the patients treated, improvement was moderate to marked; of 14 patients who were incapacitated before treatment, 9 were rehabilitated to the extent that they could resume useful occupations. A representative example of this group is Patient 1, a 57-year-old man with arteriosclerotic heart disease and an 18-month history of angina pectoris, who had been forced by progressively diminishing exercise capacity to give up his work as a laborer. During the control period of observation and the preceding several months, he experienced an average of two or three anginal pains daily in spite of marked restriction of activity. Before treatment his exercise tolerance averaged 20 trips. On being given a placebo at the outset, he showed no change in symptomatology or exercise tolerance. Administration of 160 mg. of khellin daily at this point was followed by the occurrence of only three anginal attacks in two weeks and an increase in exercise tolerance to 34 trips. Substitution of a placebo caused a return to the original frequency of anginal pains and the original exercise tolerance. Resumption of khellin therapy again induced marked improvement to the extent of the patient's having only one anginal attack in the next two weeks; at the end of this time he was able to exercise to the point of fatigue (43 trips) without pain. Continuation of therapy further reduced angina to one attack in forty-three days, enabled him to perform 54 trips on the two-step apparatus without pain and prompted him to return to work as a laborer. At the time of writing, improvement has been sustained for three months, and the patient is carrying

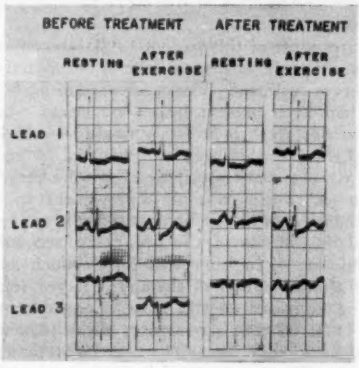

FIGURE 2. *Resting Electrocardiograms Are Similar before and after Treatment. The Electrocardiogram after Standard Exercise Shows Less Depression of the ST Segments after Treatment with Khellin. (A Return to the Pretreatment Electrocardiographic Pattern Occurred when a Placebo Was Given and Similar Lessening of ST-Segment Displacement after Exercise Resulted from a Second Course of Khellin Therapy — Case 14.)*

on a moderately strenuous occupation without difficulty.

A second patient whose course illustrates some of the phenomena observed is a 57-year-old man (Patient 2) with mild diabetes mellitus, arteriosclerotic heart disease and angina pectoris of two and a half years' duration. Six months previously, he had been hospitalized for treatment of a myocardial infarction; he had been unable to work since that time because of persistent angina on slight effort. He stated that even with considerably restricted activity, for the most part indoors, he was obliged to take three to five nitroglycerin tablets weekly for relief of anginal pain. During the control period of observation and an initial period of placebo administration, the frequency of anginal attacks did not change. With the two-step test, pain began at about 30 trips but did not force the patient to stop until 53 trips. After therapy with 120 mg. of khellin daily for three weeks, during which only three mild anginal attacks occurred,

the patient was able to perform 63 trips before pain began, and he was forced by leg fatigue to discontinue exercise while pain was still mild (77 trips). Substitution of a placebo at this point was followed by a severe relapse, 23 nitroglycerin tablets being required for control of pain within a five-day period and exercise tolerance falling to the pretreatment level. Resumption of khellin therapy again produced striking improvement, allowing the patient to return to his former job (as a night watchman) with minimal discomfort. After continuous khellin therapy for a period of three and a half months, substitution of a placebo caused no relapse: in fact, the patient has maintained his improved status up to the time of writing — that is, for two months.

The response of this patient to placebo substitution was similar to that of several other patients; it deserves comment. The occurrence of more pain than had been present before treatment when a placebo was given is probably related to continuation of the increased activity permitted by khellin, and to the anxiety precipitated by the return of symptoms. Persistence of improvement in spite of withdrawal of khellin is more difficult to explain. Cumulative effects of the drug may account for continuation of improvement for as much as two weeks after cessation of therapy; delayed relapses may be explained on this basis. Longer improvement indicates that a remission, either induced by prolonged khellin therapy or unrelated to it, has occurred; this was observed in four patients whose remissions at the time of writing had lasted two months. That such remissions may be related to khellin therapy is suggested by the fact that they occurred in patients who had previously failed to improve or had relapsed when a placebo was given; however, it is obviously possible that coincidental "spontaneous" remissions occurred in all these cases. Similar prolonged remissions have been previously observed after treatment with other medications.[23-27] The mechanism by which such remissions are induced, if indeed they are induced by therapy, is obscure. It is possible that prolonged coronary vasodilatation brings about a persistent improvement in myocardial metabolism or aids in the development of collateral circulation.

It is not surprising that nearly one third of the patients showed little or no improvement in view of the advanced coronary-artery disease present in the group; the latter is substantiated by the high incidence of previous myocardial infarctions. Other workers[28, 29] have stated that approximately 30 to 40 per cent of patients with angina pectoris do not respond to drug therapy, presumably because their collateral circulation is not capable of increased compensatory dilatation. The problem is further complicated in the case of khellin therapy by the fact that some patients are unable to tolerate therapeutic doses. One patient who experienced sustained improvement with khellin therapy again developed severe angina two months after therapy was discontinued. A second course of khellin failed to bring about appreciable improvement, presumably because of progression of the disease during the period of no treatment.

There is no doubt that large doses of khellin, or possibly impurities contained in present preparations, are capable of producing undesirable side effects in many patients. However, most patients can tolerate therapeutic amounts given postprandially in divided doses, and the incidence and severity of toxic reactions may be minimized by the use of small initial doses, with gradual increases until optimum improvement is achieved. In this study, an initial daily dose of 120 mg. for two weeks, with increments of 40 mg. at weekly intervals thereafter, was found to be a satisfactory schedule. After improvement has occurred, a smaller maintenance dose may be adequate. Whether the toxic effects are due to impurities or to the khellin itself remains to be determined; the elimination of insomnia in one patient by administration of the daily requirement early in the day suggests the possibility that this side effect, at least, is due to a rapidly excreted impurity.

Summary

Khellin, a pure crystalline derivative of the eastern Mediterranean plant *Ammi visnaga*, has been reported to have a powerful and prolonged coronary vasodilator effect in animals. Previous clinical studies indicate that it is of value in the treatment of angina pectoris.

The present investigation was undertaken to assess the effectiveness of khellin therapy in angina pectoris by carefully controlled subjective and objective methods, including the use of placebos, exercise tolerance tests and electrocardiographic studies.

Twenty-six of 32 patients were found to be benefited by khellin therapy; improvement was classified as marked in 11, moderate in 11 and slight in 4. The average therapeutic dose was 160 mg. daily; no serious toxic reactions were encountered.

The high proportion of favorable results, together with the striking degree of improvement frequently observed, has led us to the conclusion that khellin, properly used, is a safe and effective drug for the treatment of angina pectoris.

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THE PRESENT MANAGEMENT OF VARICOSE VEINS*

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RATIONAL treatment of patients with varicose veins requires exact knowledge of the changes that occur in the circulation, both venous and capillary, coincident with their development.[1] In the normal person, muscular contraction, both static and dynamic, constricts the vein, and blood is displaced in the direction permitted by the valves, that is, toward the heart. On relaxation the vein becomes filled with blood, again flowing in the direction permitted by the valves, that is, from the distal segment — a process that is associated with a lowering of venous pressure.

With the development of varices the valves are no longer competent, and external pressure on a varicose vein displaces the contents in either direction. On release of the constriction, the vein fills from above and below, and there is no effect on venous return or on venous pressure (Fig. 1).

This impairment of function, in addition to the loss of the depot function of the superficial veins of the leg and the increased blood volume necessary to fill the dilated veins, is responsible for the easy fatiguability and heaviness of which patients with varicose veins complain.[2] A less readily appreciated and more harmful accompaniment is an increased venous pressure throughout the body when the patient lies down, as pointed out by Chapman.[3] This, over a period of years, may be responsible for cardiac damage.

That serious complications and disability, however, are not more common in patients with simple varicose veins, even of large size, is due to the fact that the deep veins normally return from 80 to 90 per cent of the blood from an extremity; the addition of the 10 to 20 per cent which should be, but is not, transported through superficial veins does not greatly deplete the reserve of the deep veins. When the deep veins or veins communicating between deep and superficial venous systems in the leg become incompetent as well, there is no longer an alternate route of normal venous pressure for the return of the blood from the capillaries and venous pressure throughout the limb is elevated, with an attendant impairment in capillary function.

In the capillary, under normal conditions, fluid goes from capillary to tissue space at the arteriolar end in response to hydrostatic pressure, and from tissue space to capillary at the venule end in response to colloid osmotic pressure, but according to Landis, when venous pressure of an entire limb is elevated, or when both deep and superficial veins are incompetent (Fig. 2), there is a corresponding elevation in pressure in the capillary at the venous end and an increased filtration of fluid into tissue spaces.[4] This increased interstitial fluid, or edema, from any cause (varicose veins included) interferes with tissue metabolism (Harrison and Pilcher[5]) and is responsible for the disability and serious complications found in patients with varicose veins.

In the treatment of varicose veins the problem, in the simplest terms, is that of preventing the accumulation of excess interstitial fluid. Practically, this is accomplished by the obliteration of varicose trunks in which the pressure is continuously high, or by the application of external elastic compression. To determine which venous trunks are in-

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competent, I use a modification of the Trendelenburg test, first demonstrated to me by Dr. H. H. Faxon, and called the multiple tourniquet test (Fig. 3).[8] In this procedure, the patient lies on his back with the leg elevated, until the blood has drained from the superficial veins. Three tourniquets are then applied: one below the knee, one just above the knee and one as high as possible on the thigh. The patient then stands. If abnormally rapid filling of superficial veins occurs, it can only take place through incompetent veins communicating between deep and superficial veins in the leg. Although single incompetent communicating veins in the leg are found in patients with extensive saphenous varices of long duration, multiple incompetent communicating veins in the leg are rarely observed in patients who have not had preceding deep thrombophlebitis that has destroyed the valves of the femoral vein and in whom ligation of the superficial femoral veins distal to the profunda may be indicated, in addition to therapy directed to whatever other veins may be incompetent. In an unselected group of patients with varicose veins, those with multiple incompetent communicating veins of the leg composed 6 per cent of the total. In referred patients, this group comprises a greater proportion, for they have the greatest disability and respond least well to treatment. These patients are also the ones who should, in my opinion, continue to wear some type of external elastic compression indefinitely, since recurrence of serious difficulty is frequent.

When superficial veins fill rapidly on release of the distal tourniquet, the short saphenous vein is proved incompetent, and should be removed. Incompetence of the short saphenous vein alone occurred in 2 per cent of our patients, and it was found in conjunction with incompetence of one of the other major venous trunks in an additional 6 per cent. Eight per cent of our patients with varicose veins demanded therapy directed to the short saphenous vein.

Incompetence of a vein, other than the long saphenous vein, communicating between deep and superficial venous systems in the thigh is not common as a primary finding; it is indicated by rapid filling of superficial veins on removal of the

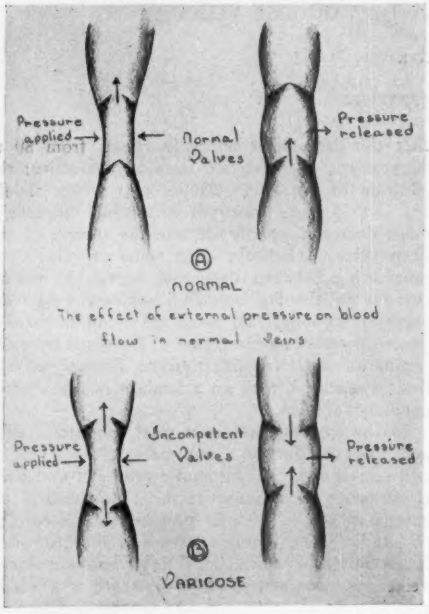

FIGURE 1. *The Effect of External Pressure on Blood Flow in Varicose Veins.*

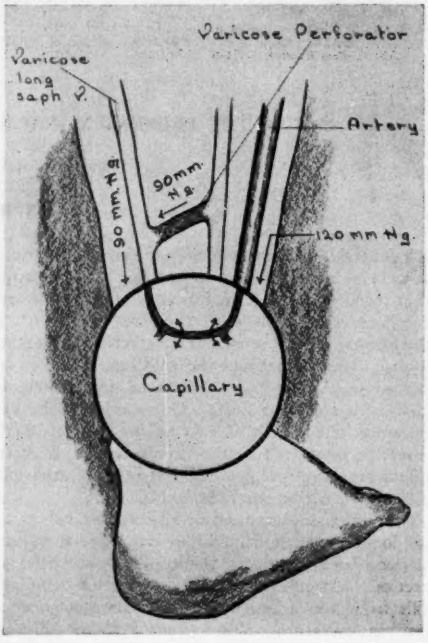

FIGURE 2. *Effect of Incompetent Perforators in Addition to Incompetence of Long Saphenous Vein on Capillary Pressure.*

tourniquet above the knee. It is, however, a frequent cause of recurrence following high ligation of the long saphenous vein, a type of recurrence that has been eliminated through subcutaneous removal or "stripping" of the vein. The remainder of the multiple tourniquet test is much the same as the Trendelenburg test; rapid filling of the superficial veins upon removal of the tourniquet in the groin indicates incompetence of the long saphenous vein, and is an almost constant finding in patients with varicose veins of any significance. In well over 90 per cent of the patients with varicose veins incompetence of the long saphenous vein has been found, either alone or in conjunction with incompetence of some other venous trunk. The exceptions were the small number in whom the short saphenous vein alone was incompetent and the few patients with multiple incompetent communicating veins due to deep thrombophlebitis. Even in this latter group, 86 per cent had incompetence of the long saphenous vein.

The results of proper treatment have been satisfactory, and are continuing to show improvement. In a group of 228 patients reviewed by Faxon and Barrow[6] in 1938, two years after treatment by high ligation and injection, 80 per cent showed satisfactory results. The failures (20 per cent) were due, in order of frequency, to poor operative technic or technical error, failure to appreciate the importance of destruction of valves of the femoral vein and multiple incompetent communicating veins in the lower leg as a factor in patients who had had preceding deep thrombophlebitis or the "natural progression of the disease."

At a later date, I reviewed a group of 169 patients who had been treated in a similar manner before 1942 and seen again in 1946. I found again that approximately 80 per cent showed a satisfactory end result. In this group, errors in surgical technic had been largely eliminated but the percentage of patients with severe and disabling varices was larger and the follow-up period longer, both of which factors tend to lower the percentage of perfect results. In a third group of 166 patients with varicose veins, treated between January, 1946, and April, 1949, a somewhat different type of treatment has been used. Since 1946, subcutaneous removal of incompetent venous trunks, or "stripping," has been almost routine, and I believe that the number of recurrences due to "natural progression of the disease" has been reduced. During the same period, we have become increasingly conscious of the importance of ligation of the superficial femoral vein in the treatment of many patients with varicose veins associated with preceding deep thrombophlebitis and multiple incompetent communicating veins of the leg.

A follow-up study of this group is hardly comparable to the preceding studies, since these patients have returned for observation at regular intervals and have been under constant supervision, and since further treatment has been given whenever indicated. In this group there is not a single patient who has had persistent ulceration, and all but a very few have had complete cosmetic and functional relief. A few older patients with edema, usually due in part at least to systemic deficiencies, principally cardiac in nature, have had to curtail

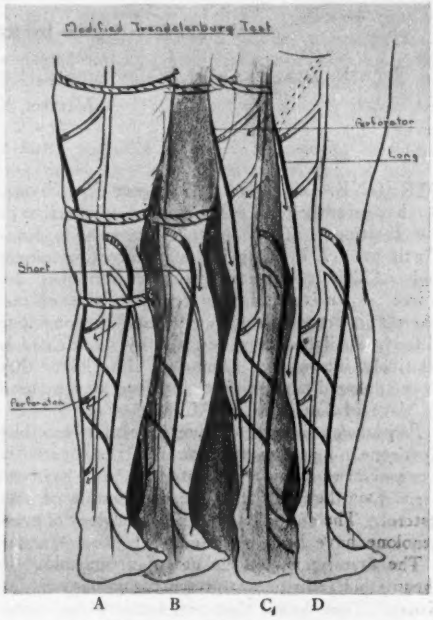

FIGURE 3. *The Multiple Tourniquet Test.*
Abnormally rapid filling with (A) *three tourniquets in place indicates incompetence of veins communicating between deep and superficial venous systems in the lower leg; with* (B) *two tourniquets in place indicates incompetence of the short saphenous vein; with* (C) *one tourniquet in place indicates incompetence of veins communicating between deep and superficial venous systems in the thigh; with* (D) *all tourniquets removed indicates incompetence of the long saphenous vein.*

their activities. The patients with preceding deep thrombophlebitis have been advised to continue to wear external elastic compression, either bandages or stockings, for an indefinite period, and fat patients have been strongly urged to reduce, for obese patients have a much higher rate of recurrence than thin ones. On the basis of these results, however, I believe that it is fair to say that practically every patient with varicose veins or concomitant complications can be relieved by appropriate treatment and persistent follow-up care.

It is also fair to say that in patients with varicose veins, as in patients with cancer, the earlier the patients present themselves for treatment and the thinner they are, or are willing to become, the more readily are such satisfactory results achieved and maintained.

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PREGNENOLONE IN RHEUMATOID ARTHRITIS*

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PREGNENOLONE (Δ 5-pregnen-3β-ol-20-one) has recently been recommended as effective in the treatment of rheumatoid arthritis.[1-5] Since Cortisone (17 hydroxy-11 dehydrocorticosterone) and ACTH (adrenocorticotrophic hormone) are scarce, expensive and not free from side effects, interest in pregnenolone is growing. Pregnenolone is freely available, may be given by mouth and is relatively inexpensive. Some of the claims that have appeared suggest that this drug may be used in place of Cortisone or ACTH.

Pregnenolone is a steroid hormone that resembles Cortisone in its structural formula. It is apparently a precursor of many related steroids,[5] and has been derived synthetically from the degradation of cholesterol.[6] The chemistry and pharmacology of pregnenolone have been reviewed.[4, 6, 7]

The first report on the use of pregnenolone in rheumatoid arthritis was presented by Davison and Koets.[1] They found that pregnenolone had beneficial effects in 8 cases (7 men and 1 woman) of ankylosing spondylarthritis. Pain and muscle spasm were relieved, and increased freedom of movement occurred. The drug was administered in doses of 50 to 150 mg. daily. During treatment, a reduction in the abnormally high level of urinary 17-ketosteroids[8] was also observed.

J. Robles Gil and F. Gomez Mont[3] studied 30 patients with rheumatoid arthritis who were given a daily intramuscular injection of 100 mg. of pregnenolone for one week, followed by a daily oral dose of 300 mg. for one month. A decrease in joint pain and local inflammation, with improvement in joint mobility and the general physical condition of the patient, was noted in 22 of the 30 patients observed (73 per cent).

Ishmael and his group[2] reported satisfactory responses in 81 of 90 patients with rheumatoid arthritis treated with pregnenolone combined with other steroids (testosterone propionate, estradiol benzoate, progesterone and testololactone). They used daily doses of 100 mg. of pregnenolone both alone and as an adjuvant of the combined androgen-estrogen regime. "In four patients, however, pregnenolone alone was more effective than testosterone propionate and estradiol benzoate, and 14 women (21 per cent) responded better to the combination of the three steroids than to androgens or to pregnenolone alone." In a study of this kind it is impossible to evaluate the therapeutic efficacy of pregnenolone except in such examples as the four arthritic patients mentioned above.

Davison and his collaborators[4] administered pregnenolone parenterally in doses of 100 to 300 mg. daily to 30 patients with rheumatoid arthritis. While the drug was given, an effective remission was induced in 10 of 12 patients; when the drug was withdrawn, symptoms and signs of active disease returned. Placebo medication was used in but 3 patients.

Freeman, Pincus and their associates[5] administered pregnenolone acetate by mouth to 30 patients with varying degrees of rheumatoid arthritis. The average daily dose was 500 mg., and the patients were observed for an average of six weeks. Fifteen patients (50 per cent) experienced striking relief characterized by a diminution of joint pain, decrease in joint swelling and an increase in functional capacity. This improvement was noted, as a rule, within a week. Eleven patients (36 per cent) showed a mild degree of improvement; only 4 patients (14 per cent) were not benefited. In 16 subjects whose treatment had been discontinued,

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We are indebted for supplies of pregnenolone and pregnenolone acetate to the Schering Corporation, the U. S. Vitamin Corporation and the Chemical Specialties Company.

Aided by a grant from the Schering Corporation, Bloomfield, New Jersey.

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improvement had been maintained for an average of six weeks. No toxic effects were observed.

Methods

Active rheumatoid arthritis was present in 25 patients. Of these, 2 patients had rheumatoid spondylitis, 3 had rheumatoid spondylitis with peripheral joint involvement, and 18 had peripheral joint involvement alone. One patient with rheumatoid spondylitis had associated acute iritis, and one had exfoliative generalized psoriasis.

In addition, 8 other patients were studied. These included 2 patients with senile osteoporosis and 1 each with tophaceous gout, acute rheumatic fever, arthralgia of unknown origin, chronic glomerulonephritis, amyotrophic lateral sclerosis and fever of unknown etiology.

The patients with rheumatoid arthritis were classified according to the standards of the New York Rheumatism Association.[9] Two patients were in Stage 1, 4 were in Stage 2, 7 were in Stage 3 and 12 were in Stage 4. There were 5 males and 20 females, ranging in age from 7 to 72 years, the average age being 50 years. Duration of the disease varied from six months to fifteen years. Two patients were bedridden (Class 4), 6 had no limitation of activity (Class 1), 8 were in Class 2 and 9 were in Class 3.

Physical examination of the patients included measurement of joint mobility, swelling and tenderness. Roentgenograms of involved joints, erythrocyte sedimentation rate, urinalysis and complete blood counts were done in all patients prior to initiation of therapy, and periodically thereafter. Eight patients were hospitalized; the remainder were followed in the Arthritis Clinic.

The majority of patients were observed for a period of fourteen weeks, including a preliminary period of observation prior to the administration of pregnenolone. Pregnenolone was given orally to 17 subjects in doses ranging from 300 to 1000 mg. daily, the average daily dose being 600 mg. Pregnenolone was administered intramuscularly to 10 subjects, in doses varying from 300 to 600 mg. daily, the average daily dose being 400 mg. Pregnenolone was administered both intramuscularly and orally to six patients, the dose varying between 300 and 600 mg., with an average dose of 400 mg. In 4 patients, the drug was given for only ten days, whereas in 2 subjects it was given for as long as 150 days. The intramuscular administration of pregnenolone was continued in all cases for at least fourteen days; in some patients therapy was interrupted because of the appearance of painful induration or inflammation at the site of injection, but was reinstituted when the reaction subsided. Pregnenolone and pregnenolone acetate were used interchangeably.

At the onset of this survey, four patients were treated with pregnenolone merely as a pilot study. All other patients were investigated by the "blind" technic. All patients received placebos at some time during this study. The identity of the medication was unknown both to observers and patients during the investigation.

Toxicity

Weight, heart rates and blood pressures were unaltered. No gastrointestinal manifestations were noted. There were no skin eruptions or prurigo. Headache was noted in 2 patients receiving pregnenolone orally in doses in excess of 600 mg. daily. It was inconstant and nonincapacitating, and disappeared when the dose was reduced to 300 mg. per day or less.

Local reactions to the intramuscular injections of pregnenolone were common. A painful induration of the buttock, which in many cases progressed to sterile abscess formation, was frequent. Two subjects required local incision and drainage of an abscess.

Results

Two of the rheumatoid arthritic patients showed marked subjective improvement. As noted on a therapeutic score card,[10] the objective improvement measured 75 per cent. In one of the two cases, a placebo was substituted after five weeks of pregnenolone; there was a rapid reversal, manifested by increase in joint pain, stiffness and tenderness. On the resumption of pregnenolone, 800 mg. by mouth was required as a daily dose before any benefits were again shown. In the other of the two improved cases, lessening of anemia occurred simultaneously with palliation of joint symptoms. In 4 other rheumatoid arthritic cases (16 per cent) questionable relief occurred. The remaining 19 rheumatoid arthritic subjects (76 per cent) derived neither subjective nor objective benefit from pregnenolone.

The patient with psoriasis showed no improvement. In the patient with spondylitis and iritis the acute iritis subsided within ten days.

The eight patients with miscellaneous ailments showed no change while on this regimen, except the patient with tophaceous gout, whose gout became worse; we attribute this, however, to cessation of colchicine administration.

Discussion

It is evident from the results obtained, whether pregnenolone is given intramuscularly, orally or in a combined form, that this drug, with the exception of two cases, was ineffective in producing significant remissions in rheumatoid arthritis. In this respect, our results are in direct variance with those reported by other observers.[1-5]

To attempt to explain the variance in results: The method of investigation may be one of the factors. We employed the "blind" technic of investigation, because we believe that the psychological reaction of both the patient under study and the physicians studying the new drug are thus reduced to a minimum.

Other considerations are the dosage of the drug and the duration of treatment. We believe that the dosage used was adequate, since it was as much as or greater than that used by others; moreover, if a satisfactory response was to occur, it should have been manifested in fourteen weeks.

Summary

Twenty-five patients with rheumatoid arthritis and 8 patients with other diseases were given pregnenolone, either orally, intramuscularly or by both routes. Dosage varied from 300 to 1000 mg. daily. Patients were observed for an average of fourteen weeks.

Two patients with rheumatoid arthritis improved; four had slight, questionable improvement but in all others no significant benefits were obtained.

Two patients developed headache, which disappeared with reduction of dosage.

After the use of intramuscular administration, painful local induration occurred regularly; sterile abscesses formed, requiring drainage, in two cases.

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HYPOPOTASSEMIA FOLLOWING BILATERAL URETEROSIGMOIDOSTOMY*

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BILATERAL ureterosigmoidostomy is frequently a concomitant of present-day urological surgery. The basic indication for this procedure is obstruction, present or anticipated, of the lower urinary tract, and most often is found in instances of tumor resection. Urologic complications and sequelae of ureterosigmoidostomy include fecal urinary fistulas and ascending urinary-tract infections with pyelonephritis and hydronephrosis.[1] Even when adequate urinary drainage is maintained, further complications may still ensue. Various insidious disturbances in electrolyte balance may appear.[2] A series of 141 cases of ureterosigmoidostomy was reported by Ferris and Odel[3]; 79 per cent of these developed varying degrees of hyperchloremic acidosis and azotemia. It has been suggested that this change in electrolyte balance is caused by reabsorption of urinary solutes from the sigmoid colon. We present here a case report of a patient who developed hypopotassemia with complete flaccid quadriplegia sixteen months after bilateral ureterosigmoid implants. No complication of this type has previously been reported.

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Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

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Case Report

A 60-year-old clerk was admitted to this hospital on May 27, 1950, for the third time, with a chief complaint of progressive and simultaneous weakness of arms and legs of three weeks' duration and quadriplegia of three days' duration. The patient had been in good health until 1941, when he entered the hospital because of gross hematuria. This was ascribed to a benign papilloma of the bladder, which was treated by suprapubic fulguration. The patient was discharged and remained asymptomatic until February, 1949, when severe hematuria recurred. At that time positive physical findings included a blood pressure of 120/90, bilateral retinochoroiditis, a suprapubic scar and a cyst of the right epididymis. Laboratory data included a red-cell count of 4,200,000, a hemoglobin of 14.9 gm., a sedimentation rate of 30 mm. in one hour, a blood urea nitrogen of 13 mg. and a CO_2 content of 53 vol. per cent, a chloride concentration of 107 milliequiv., a phenolsulfonphthalein excretion of 75 per cent in two hours, and a grossly bloody urine. Intravenous pyelograms were normal. No electrocardiogram was made. Cystogram and cystoscopy again showed a large tumor of the bladder. Accordingly, on March 8, 1949, cystectomy and bilateral ureterosigmoidostomy were performed. Pathological diagnosis was a benign papilloma. Postoperatively the patient did well, but since then he has had 6 to 8 copious watery stools daily. His dietary intake was excellent but he avoided adding salt to his food on the advice of the surgeon. Six months after operation the patient first noticed cramping leg pains with some weakness of the legs. This persisted intermittently until three weeks prior to the present ad-

mission, when he noted gradually increasing generalized weakness. Three days prior to this admission he awoke with quadriplegia and inability to perform gross bodily movements.

On admission he was moderately drowsy and disoriented. Respiration was principally diaphragmatic and obviously labored. Physical examination showed a temperature of 98.6°F., a pulse rate of 80, a blood pressure of 130/90, respirations 24 per minute and shallow. The patient was obese, pale and somewhat cyanotic, and exhibited a flaccid quadriplegia. He was unable to sit up or raise his head. His fundi showed bilateral Grade 2 changes and retinochoroiditis. There was no ptosis or dysphagia. The lungs were clear to percussion and auscultation. The heart was slightly enlarged on percussion, and the sounds were poor in quality, with a loud blowing apical systolic murmur. The abdomen was normal except for old healed operative scars. Rectal examination was negative. The right epididymis was enlarged. On neurologic examination deep-tendon reflexes were present, and no pathologic reflexes were elicited. No sensory changes were noted.

Laboratory examinations at this time showed a blood urea nitrogen concentration of 45 mg. and a CO_2 content of 24 vol. per cent, a chloride concentration of 101 milliequiv., and serum potassium concentration of 2.1 milliequiv. per 100 cc. (Table 1). An electrocardiogram showed changes suggestive of hypopotassemia with large U waves present in all leads.

Following the withdrawal of blood for laboratory studies, 1500 cc. of Darrow's solution, containing 4 gm. of potassium chloride, was given intravenously. After ten minutes of intravenous therapy a clinical improvement was noted, in that the patient was able to raise his arms. In fifty minutes the infusion was completed, and he was able to walk to the bathroom unassisted. He has since remained ambulatory.

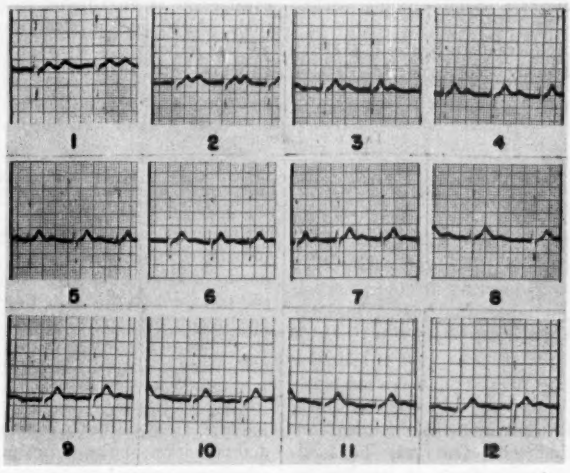

FIGURE 1. *Sections of the Continuous Electrocardiogram, Lead V_2, Taken during the Administration of 1500 cc. of Darrow's Solution Containing 0.26 gm. of Potassium Chloride per 100 cc.*

1. *Control at 9 a.m., patient showing a complete flaccid quadriplegia.*
2. *9:05 p.m., after 150 cc., patient able to raise arms slightly.*
3. *9:10 p.m., 300 cc.*
4. *9:15 p.m., 450 cc., arms moved without difficulty.*
5. *9:20 p.m., 600 cc.*
6. *9:25 p.m., 750 cc.*
7. *9:30 p.m., 900 cc., patient moved both legs.*
8. *9:35 p.m., 1050 cc.*
9. *9:40 p.m., 1200 cc.*
10. *9:45 p.m., 1350 cc.*
11. *9:50 p.m., 1500 cc.*
12. *9:55 p.m., 10 cc. of 10 per cent calcium gluconate IV. Patient left his bed and walked to the bathroom unassisted. Electrocardiogram shows a progressive return to normal with a decrease in the QRS interval and a gradual diminution of the U waves. Final serum potassium 2.46 milliequiv.*

An electrocardiogram made after the administration of the potassium chloride showed an almost complete reversal of the abnormal electrical findings (Fig. 1), despite the fact that the serum potassium concentration at this time was only 2.46 milliequiv. Other laboratory determinations made since completion of the aforementioned therapy are shown in Table 1. Skeletal surveys showed a minimal degree of generalized osteoporosis, with no pseudofractures. Intravenous pyelograms showed fair concentration of the dye, with calyceal systems outlined about as well as prior to surgery. Beginning on June 11, 1950, the patient was given orally 3 gm. of sodium bicarbonate daily until June 20, 1950, when minimal ankle edema appeared, his serum electrolyte concentrations having returned to normal. After the initial therapy, he remained entirely asymptomatic throughout his remaining hospital stay.

Discussion

Hypopotassemia occurring in chronic nephritis has been described.[4] A plausible sequence of events in this case would be ascending urinary infection secondary to ureterosigmoidostomy, with resultant renal tubular damage. Subsequently, this inability to excrete acid urine or to synthesize ammonium led to acidosis and dehydration, with compensatory excretion of potassium as a sodium-sparing mechanism.

Hypopotassemia produces disturbances in skeletal muscle, which consequently becomes flaccid. Paralysis of the diaphragm and intercostal musculature causes respiratory difficulty that may be fatal. The cardiovascular manifestations, as described by Frenkel and others,[5] include increase in pulse pressure, low diastolic pulse pressure, collapsing pulse, increase in cardiac dullness, systolic murmur, ectopic rhythms, high venous pressure and marked electrocardiographic changes. The electrocardiographic changes have been classified by Bellet and his coworkers[6] in five patterns: 1. ST-segment depression accompanied by lengthening of the QT interval. 2. T-wave inversion and QT-interval prolongation, frequently followed by a U wave. (There are three types of T-wave inversion: inversion of the T wave with elevation of the initial portion of the ST segment followed by a downward dip, inverted T wave situated below the isoelectric line and inverted T wave with prolongation of the QT segment.) 3. Upright T waves and prolonged QT interval with the T wave occupying the entire QT segment. 4. T wave almost isoelectric, and accompanied by a terminal U wave. 5. Normal T wave followed by an unusually prominent U wave without prolongation of the QT interval.

This case shows that hypopotassemia may complicate ureterosigmoidostomy and should be considered in the postoperative management of these patients. It also illustrates the value of the electrocardiogram as an adjunct to chemical determinations. Although the electrocardiographic findings are an important criterion of hypopotassemia in patients with suspected disorders of electrolyte balance, they are not a substitute for the chemical determination of the serum potassium. Therefore, adequate chemical studies must not be omitted, as much essential evidence can be obtained only by this means.

Table 1. *Laboratory Data.**

Date	Blood Urea Nitrogen	Carbon Dioxide	Chlorides	Calcium	Phosphorus	Potassium	Sodium	Creatinine	Acid Phosphatase	Alkaline Phosphatase	Red-Cell Count	Hemoglobin	White-Cell Count	Phenol-Sulfonphthalein Excretion
	%	*vol./100 cc.*	*milliequiv./liter*	*mg./100 cc.*	*mg./100 cc.*	*milliequiv./liter*	*milliequiv./liter*	*mg./100 cc.*			*x10⁶*	*gm./100 cc.*	*x10³*	%
3/1/49	13	53	107						1.9 GU†	3.2 GU	4.2	14.9	7.4	75/2 hr.
5/28/50	45	24	101	9.2	3.4	2.17	141.2	3.9			3.8	12.8	10.0	
5/29/50	41	26	92			2.46	139.7		0.5 SU‡	7.7 SU	3.8	12.9		
6/20/50	18	60	97	10.7	2.2	4.16	142.2	1.9	0.5 SU	9.3 SU	4.4	14.6	5.0	15/15 min.

*Therapy included 3 gm. sodium bicarbonate (orally) daily, 6/11–6/20 and a whole-blood transfusion of 500 cc. on 6/19.
†Gutman units.
‡Shinowara units.

The authors are indebted to Dr. Julius Wolfe for valuable assistance in the study of this patient.

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FIFTY YEARS OF MEDICAL PROGRESS

MEDICINE AS A SOCIAL INSTRUMENT: PREVENTIVE MEDICINE*

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IN ANY consideration of preventive medicine, one encounters a difference of concepts of the subject matter under discussion. What does the field of "preventive medicine" include? What functions of medicine does it encompass? Does it mean the same thing to everyone? How has its meaning changed in fifty years?

For the purpose of this discussion, I have arbitrarily decided that preventive medicine shall include as its responsibility all those matters that deal with the prevention of illness and the promotion of health *of the individual.* This is in contrast to the function of "public health," which encompasses the activities of the community in the promotion of the health *of the community* as a unit. The aims and objectives of preventive medicine and public health are the same, but the allocation of responsibilities is quite different. The community is interested in the individual only insofar as his health and welfare affect the community as a whole.

Preventive medicine, on the other hand, concerns the individual directly. It is, essentially, the responsibility of the practitioner of medicine, who undertakes protection and promotion of the health of those individuals and their families who have entrusted themselves to his care.

This concept of preventive medicine is a very old one. Edward Jarvis, a Boston physician (1803-1881), was one of the first to emphasize that preventive medicine should be an integral part of medical practice.

> Our education has made our calling exclusively a curative, and not a conservative one, and the business of our responsible lives has confined us to it. Our thoughts are devoted to, our interests are concerned in, and our employments are connected solely with, sickness, debility, or injury, — with diminution of life in some of its forms But with health, with fullness of unalloyed, unimpaired life, we, professionally, have nothing to do. Yet the intelligent physician can see arrows of disease, invisible to anyone else; watch their havoc, and know whence they come, and how they may be stayed; and there are many eminent medical men who have, as individuals, nobly used the means which their superior position and knowledge have placed within their control, in the *prevention* of *disease,* and in the promotion of public health. And we wish to increase the number of such professional men.†

It is clear that the application of preventive measures in clinical practice by physicians during the past century was limited in scope. Because disease was believed to be due, for the most part, to environmental factors (bad air, bad odors, impure water, and miasmata of all types), preventive medicine became primarily a matter of environmental sanitation and personal hygiene — or, more simply, community and personal cleanliness.

This was true even at the beginning of the year 1900. The state and the local communities had not yet begun to pursue aggressively their responsibilities in the promotion of community health services, and public health as it is now understood was then only being initiated. The practicing physician was the major force in the promotion of public-health activities.

What did preventive medicine mean at the beginning of the century? Fortunately, we have an excellent source of information on this point. President Eliot of Harvard was one of the first to insist upon the necessity of teaching preventive medicine as an integral part of the medical-school curriculum. In 1909 he selected Dr. Milton J. Rosenau, of the United States Public Health Service, as the first full-time professor of preventive medicine in Harvard Medical School. Dr. Rosenau was a great leader in this field in his generation, and his concepts and teaching represent the best thinking of the early part of the century. Therefore it seems most appropriate to use, in considering preventive medicine at the beginning of the century, the concepts of this subject as presented by Dr. Rosenau‡ in the first edition of his textbook.

He defined the field as follows: "Preventive Medicine (and Hygiene) may be considered in two parts, namely: (a) that which deals with the person (hygiene); (b) that which deals with the environment (sanitation). The first part includes prevention of communicable disease, venereal prophylaxis, immunity, heredity, etc."

Dr. Rosenau's original course of medical-school training put great emphasis on environmental sanitation: water supply, disposal of sewage and gar-

*From the Department of Preventive Medicine and Public Health, Cornell University Medical College, New York City.

†Quoted by Lemuel Shattuck in The Massachusetts Sanitary Commission Report, 1850.

‡Rosenau, M. J. *Preventive Medicine and Hygiene.* 1102 pp. New York: D. Appleton & Co., 1913.

bage and sanitation of milk and other foods. These were regarded as vehicles of infection. Disinfection, quarantine and isolation were also emphasized. He gave an extensive discussion of preventive measures in control of typhoid fever, smallpox, diphtheria, scarlet fever and other communicable diseases of childhood. Malaria control was stressed. Diseases particularly related to social conditions, such as tuberculosis and syphilis, were given serious consideration, but malnutrition was not mentioned, and there was no discussion of housing in its relation to health. Dr. Rosenau, at that early period,

FIGURE 1. *A Three-Dimensional Graph Showing the Almost Complete Disappearance of Summer Diarrhea in Massachusetts by 1930.*

had a keen insight into the importance of occupational diseases, and he also gave serious thought to medical inspection of schools. There was a chapter on immunity, and one on heredity and eugenics. A few paragraphs were inserted on the prevention of mental disease (by Thomas W. Salmon).

This brief summary of Dr. Rosenau's first text gives us, in concise form, the most advanced ideas about preventive medicine at the beginning of the twentieth century. His ideas were sound. His textbook answered the needs of the day, and was a strong foundation on which to build for the future.

Using these ideas as our base line, we can measure the changes that have occurred in the field of preventive medicine, and the advances that have been made during the past fifty years.

Environmental Sanitation: A Public-Health Function

The proper sanitation of the home and of the community has become, during the past fifty years, a definite community responsibility. Great advances have been made in the sanitary technics used in community water supplies, sewage disposal plants, housing, recreational facilities, food sanitation and so forth. These developments have been made along engineering lines; they have not been the responsibility of the physician. Furthermore, the physician has not played a great part in the extraordinary reduction of illness and death that has resulted from these effective community-wide measures of health protection. The development of sanitation, which was considered a major factor in preventive medicine in 1900, is now accepted as an almost exclusive function of public-health supervision; it is the province of state and local sanitary engineers and their staffs. These activities have contributed more to the reduction of the death rate during the past fifty years than has any other single factor, and they are the best developed of all our public-health activities. Furthermore, the technical revolution in the refrigeration, processing and storage of food and the rapid transportation of fruit and fresh vegetables, as well as the growth of markets and the improvements in the technics of plant and animal husbandry, have resulted in an almost incredible improvement in the nutrition of people of all economic levels.

Communicable-Disease Control

The diseases to which Dr. Rosenau gave greatest consideration in his discussion of preventive medicine fifty years ago (smallpox, typhoid fever, malaria, bacillary dysentery, diphtheria, scarlet fever, typhus fever and so forth) have practically disappeared from the statistical tables of morbidity and mortality. Malaria has so completely vanished from its old haunts that it has been almost impossible to find a person newly infected with malaria in the entire United States in the year 1950. Many states have no more than one or two deaths from typhoid fever per year. Bacillary dysentery and other intestinal infections — and particularly diarrheal diseases of childhood — have been wiped out in one generation (Fig. 1). But it must be remembered that most of these triumphs have been achieved through public-health measures, and not by application of the principles of preventive medicine.

The physician, in carrying out typhoid vaccination or diphtheria and smallpox immunization for protection of his patients, has been an effective aid. In recent years, the use of antibiotics has done much to prevent bacillary dysentery, and death from streptococcal infections and lobar pneumonia. On the whole, however, the great achievements during the past fifty years in the reduction of communicable diseases must be credited to *public health* — that is, to community-wide health-promotion measures.

The Venereal Diseases

Extensive efforts have been made to prevent and control the venereal diseases during the past fifty years. Progress was slow during the first quarter-century, and public-health efforts were signally unsuccessful. The discovery of the cause of syphilis and the introduction of the arsenicals as therapy reduced cerebral syphilis together with other late and severe manifestations, but treatment was so tedious and expensive that physicians were glad to turn their cases over to the community clinic. Furthermore, infectious cases were difficult to sterilize, and spread of infection occurred even when the patients were under active treatment. A great service in public education was rendered in the elucidation of the epidemiology of the disease, but control measures were quite ineffective. The revolution in the prevention of venereal diseases has occurred so recently that one cannot yet appreciate its full import. It is now certain that the newer methods of rapid and effective treatment of both gonorrhea and syphilis are strikingly effective in disease prevention. Gonorrhea is no longer a public-health problem. It can be cured even before a report of contagion can reach the health officer. A case of infectious syphilis can be rendered non-infectious within a few hours; the major clinical problem is reinfection of the cured syphilitic, rather than the relapse of uncured cases. Transfer of infection is mimimized, because the infectious patient can be sterilized so readily. Patients are now treated in the offices of physicians, and most public clinics may soon be closed.

Tuberculosis

In 1900, this disease was the leading cause of death. In our larger cities, there were more than 250 deaths from pulmonary tuberculosis per 100,000 population. By 1950 this figure had dropped to about 30 per 100,000. The rate still varies greatly in different sections of the country. Some entire states — Wyoming and Idaho, for example — have rates below 10, whereas some restricted Negro sections of our larger cities still have death rates of over 200 per 100,000. No one can truly evaluate all the factors that are responsible for this extraordinary conservation of life throughout the nation. Undoubtedly, broad and general social factors have played the largest part. These include better education, better housing, better food, improved living conditions and so forth. Most important of all, perhaps, has been a true understanding of the epidemiology of the disease, and of its cause, nature and prevention. For few people even realized, fifty years ago, that tuberculosis was an infection that was transmitted from a sick person to his associates.

We have every reason to believe that tuberculosis will continue to decline as a cause of illness and of early death. But the decline will not be secured through mass x-ray examinations of large unselected numbers of people, nor through the construction of bigger and more numerous sanatoriums. The technics of detection, prevention and control of tuberculosis have reached the stage where these measures should be carried out as an essential part of medical practice, as opposed to attacking the disease primarily by mass-control procedures. Only by a judicious and well co-ordinated program of public-health supervision and preventive medicine can the best results be secured.

MATERNAL AND CHILD HEALTH

It is almost impossible to realize that the whole field of pediatrics, including the concepts of maternal and infant health protection, has been developed within the past fifty years. Except for a brief discussion of school inspection, Rosenau's early text on preventive medicine does not even mention child hygiene. In 1900 the infant-mortality rate in New York City was 135.3 per 1000 live births; the maternal mortality rate was 5.8. The 1950 rates were 24.9 and 0.7 respectively.* This decline is undoubtedly the outstanding achievement of preventive medicine during the past fifty years. Part of this saving of life has been due, directly or indirectly, to the public-health activities of the community. Milk pasteurization, health education, well-baby clinic service, public-health nursing and many other community activities — all have played an important part in the reduction of illness and death in childhood. But there can be no question that the individual care of mothers and babies by skilled and well trained physicians has been the key to the tremendously successful results that have been achieved in health promotion

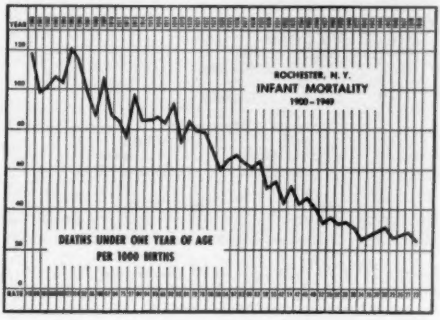

FIGURE 2. *A 50-Year Decline in Infant Mortality in Rochester, New York.*

The data are representative of the nation (Reproduced by courtesy of the Health Department, Rochester, New York).

*From the *Preliminary Report of the New York City Health Department for 1950.* This example is selected because it is fairly representative, and because 1950 data are available.

and in the protection of mothers and children. Today the efficient pediatrician practices preventive medicine almost exclusively. He is the one who has shown his fellow practitioners how preventive medicine can and must be incorporated in day-to-day medical practice in any plan of adequate medical care.

Adult Health Promotion

The higher rate of survival of infants and children has created new problems in preventive medicine. Our population ratios have been greatly modified, and our pattern of family life has changed. The saving of babies' lives has resulted in an aging population, with all the special conditions and particular diseases that pertain to eventual decay. For the babies that have been saved grow up to live longer, and to die eventually of degenerative disease.

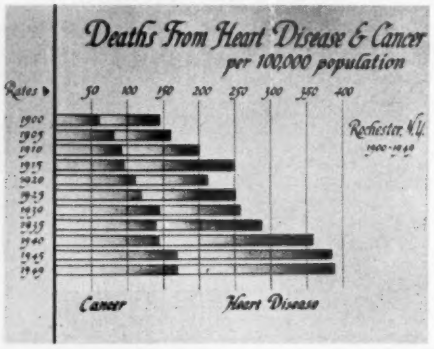

Figure 3. *A 50-Year Increase in Deaths from Heart Disease and Cancer in Rochester, New York (Reproduced by Courtesy of the Health Department, Rochester, New York).*

No consideration was given to adult health protection in 1900, other than in the field of industrial hygiene. No mention is made in Rosenau's early text of preventive measures for heart disease, cancer, diabetes or rheumatism, or for the conservation of hearing and of eyesight, or for early detection of glaucoma or hypertension. These matters were left for future consideration.

By 1950, heart disease was by far the most common cause of death; cancer and other degenerative diseases were well in the vanguard. An appreciation has developed, gradually, of the necessity for the application of the principles of preventive medicine to the treatment of degenerative diseases. The physician follows the general pattern used in communicable disease control. That is, he investigates the etiology of these diseases, devises methods for early detection of the disease and brings the patient who is in the initial stages of the disease under medical care as early as possible.

Attempts have been made, through organized community efforts, to apply the principles of public health to the control of degenerative disease and to develop mass methods for the early detection of various types of chronic illness. "Multiphasic screening tests" have been organized chiefly under Health Department agencies and also under voluntary auspices for an appraisal of presumably normal persons, in an attempt at early detection of chronic disease. In multiphasic screening, as often carried out, normal adults are first given a series of tests by skilled technicians. The results are assembled and reviewed by a physician; if positive findings warrant it, the subject is referred to his physician for further study. The great difficulty in multiphasic screening is that the interpretation of a series of diagnostic tests is of little value without an understanding of his personality and a familiarity with his history and family background.

Table 1. *Ten Leading Causes of Death in New York City.*

	Deaths per 100,000
1900	
Pneumonia	304.2
Tuberculosis	279.5
Diarrhea and enteritis	183.1
Nephritis	161.1
Heart disease	128.2
Accidents	87.1
Apoplexy	80.8
Cancer	66.5
Ill defined and unknown	64.7
Diseases of early infancy	59.5
1950	
Diseases of the heart	437.5
Cancer	195.4
Vascular lesions of central nervous system*	64.9
Diseases of early infancy	39.7
Accidents	37.0
Pneumonia	32.3
Tuberculosis	29.2
Diseases of liver and gall bladder	22.2
Diabetes	20.1
Diseases of the arteries	15.8

*Mainly apoplexy.

The person should not go first to the health center for multiphasic screening and then be sent to his physician. He should see his physician first and be referred by him to the health center for the necessary diagnostic tests.

Early detection of degenerative disease cannot be properly done through conventional public-health "mass procedures." The physician who is trained to incorporate preventive medicine with routine practice is the one who is responsible for early detection of all types of degenerative disease. This requires a system of periodic physical examinations for adults, following the practice now generally used for infants and children. It can be developed best, for the average man, under a system of prepayment for comprehensive medical care, since most persons will not voluntarily seek and pay for the services of a physician while they are well.

Incorporation of Preventive Medicine as an Integral Part of Medical Care

The most important concept of the century in the field of medical care is the idea that preventive medicine is an integral and necessary part of the everyday practice of medicine. It is not a

separate body of knowledge to be understood only by a skilled technician who has been highly trained in this field. There is no "specialty" of preventive medicine, as there is a specialty of surgery, radiology or pediatrics. There is, of course, a specialty of public health, which is a well organized body of knowledge and requires a high degree of skill. But preventive medicine must function in conjunction with diagnosis, treatment and rehabilitation. These are the four basic elements of every physician's continuous plan of medical care for each of his patients.

All great physicians of all times have understood and acted upon the principle that the practice of medicine is not simply an exercise in diagnostic acumen, nor a test of therapeutic skill, but a complete understanding of a patient as a person — as one who is a member of a family, and who lives in a circumscribed environment that has a profound influence, for better or for worse, on his health. The great physicians have also understood and followed the principle that every person is entitled to the benefits of preventive medicine as an essential part of his medical care.

The reawakening of our appreciation of this fundamental idea is, I believe, the greatest advance in the concepts of medical care of this half-century.

1300 York Avenue

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 37091

PRESENTATION OF CASE

First admission. A thirty-seven-year-old man entered the hospital complaining of swelling of the left side of the neck.

The patient had been in excellent health until seven months prior to admission, when he first noted painless swelling of the left side of the neck and discrete lumps under the skin near the clavicle. Two months before admission dilated veins appeared over both sides of the chest, extending down as far as the sternum; moderate edema of the face was noted. A biopsy was performed on a supraclavicular lymph node at another hospital and reported as "hyperplasia." Following this operation, the edema of the face increased, resulting in partial closure of the left eye, and the patient was referred to this hospital for further study.

Twenty-five years previously an appendectomy was performed. A "fatty tumor of the thigh" was removed twenty years before entry. There had been two brief episodes of painless hematuria one month before admission. The patient habitually drank a quart of milk a day.

On physical examination the face was puffy, plethoric, and slightly cyanotic. There was brawny nontender swelling of the left lower cervical region and a compressible, nonpulsatile tender swelling above the suprasternal notch. The superficial chest veins were uniformly distended. The thorax showed moderate right scoliosis. On both sides of the chest posteriorly above the midpoints of the scapulas there were heard dullness, bronchial breath sounds, decreased breath sounds and increased whispered voice sounds. No rales were heard. There were Grade II apical and pulmonic systolic murmurs. The liver was felt two fingerbreadths below the costal margin on deep inspiration.

The blood pressure was 125 systolic, 70 diastolic.

The urine had a specific gravity of 1.012 and contained no albumin; the sediment contained rare red cells, rare white cells and a few granular casts per high-power field. Examination of the blood disclosed a hemoglobin of 16.5 gm., a red-cell count of 4,400,000, and a white-cell count of 5500, with 59 per cent neutrophils, 33 per cent lymphocytes, 5 per cent monocytes, 2 per cent basophils and 1 per cent eosinophils. The platelets appeared normal. The nonprotein nitrogen was 27 mg., the alkaline phosphatase 4.2 units and the phosphorus 1.8 mg. per 100 cc. An intravenous pyelogram was unremarkable. Chest films showed a lobulated mass of homogeneous density lying anteriorly in the superior mediastinum and extending bilaterally from just above the manubrium to below the pulmonary artery, displacing the trachea posteriorly and the esophagus slightly to the left (Fig. 1). The lung fields were clear and the heart and aorta unremarkable. A biopsy of a left cervical lymph node was interpreted as diagnostic of metastatic carcinoma; the patient was discharged to be followed in the Tumor Clinic.

Second admission (four years later at age 41). The patient received 6000 r of deep x-ray therapy to the mediastinum and 1000 r to the left supraclavicular area with good results, although palpable lymph nodes remained after treatment and a diminished mediastinal mass was still demonstrable

on x-ray examination. For one year he was virtually asymptomatic. Three years before the second admission, during a coughing spell brought on by a cold, there was a sudden onset of severe, sharp, nonradiating midline lower-abdominal pain, followed by passage of a small amount of bloody urine. A similar attack of hematuria occurred four days later. The urine at this time gave a + test for albumin, and the sediment was loaded with red cells. Cystoscopic examination, intravenous pyelograms and a barium-enema examination were negative. Rectal examination revealed a firm mass in the left lobe of the prostate, which was thought to be inflammatory. Two and a half years before

FIGURE 1.

admission chest plates showed an increase of approximately 50 per cent in the size of the mediastinal mass. Four thousand r of further radiation was directed to the mediastinum, but this produced little regression. Two years before admission firm nodes appeared in the left axilla, and as these increased in size the patient was given 2100 r of radiation to this region, with resultant regression of the nodes to half their original size. Fourteen months before admission there was another attack of painless hematuria; one month later the patient again had bloody urine, this time accompanied by midline lower-abdominal pain. Intravenous pyelograms were again negative; cystoscopy showed diffuse inflammation of the bladder wall, trigone and ureteral orifices. One year prior to admission the basal metabolic rate was −19; the calcium was 11.8 mg., the phosphorus 2.6 mg. and the alkaline phosphatase 5.6 units per 100 cc. A third course of 6000 r of radiation was given to the mediastinum at this time because of x-ray evidence of enlargement. This was followed by postprandial nausea, which subsided after one month. Six months before admission the blood calcium was 12.0 mg., the phosphorus 2.2 mg. and the alkaline phosphatase 6.0 units per 100 cc. Radiation pneumonitis was demonstrable in the x-ray films, but the patient had no pulmonary complaints. Forty-one hundred r of radiation was directed at the left supraclavicular region at this time because of enlarging lymph nodes. Two months later the calcium was 11.0 mg., the phosphorus 2.6 mg. and the alkaline phosphatase 5.0 units per 100 cc. At about this time the patient began to have intermittent severe headaches, marked exertional dyspnea and two- to three-pillow orthopnea. Skull plates were negative; dental films failed to reveal any demineralization of the lamina dura.

Two months before admission the patient noted the onset of sharp pleuritic pain over the left lower half of the sternum, which became sufficiently severe to embarrass respiration and cause sweating. The pain responded to morphine. Physical examination revealed a friction rub in the left midanterior chest. An electrocardiogram showed elevation of the ST segments in Leads 1, 2 and V_6 compatible with an early infarction or pericarditis. Serial records showed resolution compatible with an active process. An ear, nose and throat examination revealed no cause for the repeated headaches. The second admission was occasioned by increasingly severe orthopnea and by ankle edema first noted four days previously.

On physical examination a pleural effusion extending to the level of the ninth thoracic vertebra was demonstrable bilaterally. Both borders of the heart appeared enlarged on percussion. The heart sounds were of fair quality, with a regular rhythm at a rate of 130 and protodiastolic gallop. No murmurs or rubs were heard. The blood pressure was 122 systolic, 98 diastolic in the right arm and 116 systolic, 90 diastolic in the left. The liver was percussed six fingerbreadths below the costal margin, but no edge was felt. Abdominal tenderness was marked in the right upper quadrant, minimal in the left upper quadrant. There was +++ pitting edema of the extremities.

The urine had a specific gravity of 1.012 and gave a ++ test for albumin and a strongly positive Sulkowitch reaction; the sediment was loaded with red cells. Examination of the blood revealed a hemoglobin of 13.9 gm. and a white-cell count of 11,600, with a normal differential. The nonprotein nitrogen was 23 mg., the total protein 6.0 gm. with an albumin-globulin ratio of 1.8, the calcium 10.6 mg., the phosphorus 2.3 mg. and the alkaline phosphatase 6.1 units per 100 cc. Twenty-four-

hour calcium excretions were 237 and 284 mg. Intravenous pyelograms showed areas of calcification overlying both kidneys and a third area of calcification on the left side of the pelvis; these were interpreted as bilateral renal and left-ureteral stones. Cytological examination of the pleural fluid showed malignant cells, although their existence was not confirmed by pathological examination of a cell block.

The patient did not respond to digitalization and mercurial diuretics, but noted marked subjective relief of the dyspnea after chest taps. He was given five intravenous injections of nitrogen mustard (6.6 mg. in saline solution) and was again discharged to the Out Patient Department.

Final admission (eight months later). The patient was maintained on a low-salt diet, ammonium chloride and mercurial diuretics. An immunizing course of parathormone was given without significant clinical improvement or change in blood chemical findings. In the three months prior to the third hospital admission the patient was admitted four times to the Emergency Ward with complaints of severe pleuritic distress, dyspnea and edema; he was treated with oxygen, aminophylline, and chest taps. However, the patient remained at work throughout the entire illness with the exception of the periods of hospitalization. The third admission was also occasioned by dyspnea.

On physical examination the neck veins were distended at a 90° angle. Hard lymph nodes were palpable in both axillas and in both anterior cervical chains. The skin of the neck was deeply pigmented and the trachea fixed. Loud bronchial breath sounds were heard posteriorly on the right. There were signs of fluid at both lung bases, with scars of old thoracenteses. There was marked sacral edema, and pitting edema of the lower legs.

The temperature was 98°F., the pulse 120 and the respirations 28. The blood pressure was 120 systolic, 100 diastolic.

The urine had a specific gravity of 1.018, was negative for albumin and gave a +++ Sulkowitch reaction; the sediment consisted of a very large number of hyaline casts, 4 to 8 red cells and 2 to 4 white cells per high-power field. Examination of the blood showed a hemoglobin of 16.5 gm. and a white-cell count of 10,200, with a normal differential. The nonprotein nitrogen was 27 mg., the total protein 5.6 gm., with an albumin-globulin ratio of 2.1, the calcium 11.6 mg., the phosphorus 2.7 mg. and the alkaline phosphatase 10.7 units per 100 cc.; the sodium was 132 milliequiv., the chlorides 95 milliequiv. and the carbon dioxide 35 milliequiv. per liter. An x-ray film of the chest showed a right hydropneumothorax and a probably paralyzed diaphragm on the left. There was a large tumor mass in the mediastinum and very extensive fibrosis of both lungs. The heart was not enlarged. Sputum cultures contained abundant alpha-hemolytic streptococci and a few colonies of *Staphylococcus aureus* but were negative for beta-hemolytic streptococcus and pneumococci.

Repeated thoracenteses yielded straw-colored, slightly cloudy fluid with a specific gravity of 1.012; this contained 1.8 gm. per 100 cc. of protein but no malignant cells on cytological examination. The patient continued to have extreme dyspnea in spite of chest taps and oxygen. A course of three intravenous injections of 12.6 mg. each of nitrogen mustard in saline solution was given on the second, third and fifth hospital days but produced no appreciable change. The patient was preparing to go home on the seventh hospital day when he suddenly became confused and extremely cyanotic and fell out of bed. He died two minutes later.

Differential Diagnoses

Dr. John B. Stanbury*: I should like to see the x-ray films first, Dr. Wyman. I am particularly interested in knowing if there is any evidence of bone disease. I should like also to know about the renal shadow and the size of the heart.

Dr. Stanley M. Wyman: I have tried to select a few films from the very large number on hand. One of the earlier films demonstrates a large nodular mass in the superior mediastinum, lying anteriorly (Fig. 1). The esophagus is somewhat displaced, showing that there is enlargement of lymph nodes in the region of the carina. The heart shadow itself appears well within normal limits, and the lung fields appear grossly clear in the early phase of the disease. One of the films taken after the first course of treatment discloses remarkable reduction in the size of the mass. Films taken two years later show a rather characteristic rectangular area of scarring and fibrosis in the center of the lung, due to the heavy radiation he received. At this time the mass is also quite small. Subsequent films show no appreciable change, excepting the last film, in which the changes are more severe, with increased fibrosis and possibly increased size of the mass. The diaphragm is elevated on the left, and there is fluid on the right. The bones of the chest appear normal. Two films selected from the last pyelogram show stones in both kidneys and a definite stone in the left lower ureter. The bones of the lumbar spine and pelvis appear normal. In a film of the teeth the lamina dura seems well preserved. The skull shows a relatively normal bony texture throughout the calvarium. There are none of the typical stigmata of hyperparathyroidism.

Dr. Stanbury: We have three problems here. The first is to account for the metabolic disorder and its consequences, the second, to account for the mediastinal lesion and its consequences and the third, to decide whether there was a relation between the two.

*Assistant physician, Massachusetts General Hospital.

I should like to discuss first the metabolic disorder. The first suggestive symptom was hematuria, which occurred one month before the first admission. At the time of admission the patient had microscopic hematuria, which, if one wished to make a diagnosis of hyperparathyroidism ultimately, might suggest that the disease had been present for a long time and had led to a stone that he had passed. It was at this time that the phosphorus of 1.8 mg. was discovered, but this was not followed up. It was not until approximately three years later that further account was taken of the metabolic disturbance. One year before the second admission the blood chemical determinations, made because of repeated bouts of hematuria, disclosed on three successive occasions an elevated calcium, depressed phosphorus and a normal alkaline phosphatase. Several intravenous pyelograms showed no evidence of renal disease. However, he did have a ++ test for albumin and a positive Sulkowitch test on the second admission. The serum calcium again was slightly elevated, and the phosphorus depressed; the increased excretion of calcium reflected only an elevated blood calcium. About a year before death there was calcification of both kidneys and pelvic ureteral stones. Eight months later, after a course of parathormone, he was still excreting more than a normal amount of calcium, he was still having microscopic hematuria, the calcium was still elevated, the phosphorus was still depressed and the phosphatase was decidedly elevated.

There are several aspects of this metabolic disorder that I should like to point out. He had no evidence of bone disease, and the lamina dura was intact. In bone disease occurring in the course of hyperparathyroidism, destruction of the lamina dura is frequently the first sign. Furthermore, he did not develop any noteworthy degree of renal insufficiency, and shortly before death the nonprotein nitrogen was normal. There was no mention of hypermobility of the joints, of bone pains or of any protracted periods of nausea. He developed no metastatic calcification. In short, he never had any symptoms suggestive of hyperparathyroidism. I should like to suggest that the metabolic disorder of this patient was of a mild degree and was probably not contributory to the mainstream that led to his death. Nevertheless, I have to account for the blood chemical findings and the recurrent renal stones. The simplest way is to assume that he had a parathyroid adenoma incidental to the other disease.

Another disease that would account for it is parathyroid carcinoma, a very rare condition. Two years ago Dr. Norris,[1] of the Department of Pathology, reported 15 cases of parathyroid carcinoma that he had collected from the literature and from this hospital. Only three of the patients actually had died, and only two of the deaths could be attributed to the hyperparathyroidism. It does not seem to be a generally fatal disease. Practically all these patients had very small tumors. Only one or two had tumors of a size similar to this tumor. Furthermore, all the patients who had changes in the blood calcium and phosphorus had severe bone disease. This patient had no bone disease. I consider a diagnosis of parathyroid carcinoma most unlikely.

There is one other possible way to explain changes of the calcium and phosphorus: metastatic malignant bone disease. From time to time elevated blood calcium and depressed blood phosphorus values have been reported as associated with metastatic carcinoma of the breast, prostate, lung, thyroid and kidney, and with myeloma. Usually, when metastases from these origins occur, the calcium is elevated and the phosphorus is normal or elevated; the explanation for the elevated calcium and depressed phosphorus in such cases is obscure. Dr. Albright[2] reported a case of hypernephroma that was followed for three years with repeated x-ray treatments. Prior to x-ray therapy the calcium would be high and the phosphorus low, and after x-ray therapy they would return to normal for a while. I have to accept the fact that in certain cases of carcinoma of various cellular origins the calcium is elevated and the phosphorus is depressed. However, in all such cases that I have found, no evidence of bone disease was noted.

Now we may discuss the mechanical problem. The patient entered the hospital with a large superior mediastinal tumor that obstructed venous return from the head. He responded over the course of years to intensive radiation therapy, and finally died as a consequence of the mechanical condition in the superior mediastinum. The first biopsy performed before he came to the hospital showed hyperplasia, and the second showed carcinoma. This troubled me greatly, but I shall have to accept the fact that the patient had a biopsy that was consistent with metastatic carcinoma. Then there is the curious fact that he had axillary masses. It is most unusual to find axillary masses metastatic from visceral carcinoma. Such masses are usually metastases from the breast and the lung. I have just learned of one case in which they came from the thyroid gland. Another thing I should like to call attention to is the compressibility of the tumor in the left side of the neck. Was it compressible in the sense that it was a vascular tumor, or did it simply slip down through the superior cervical strait? If it was really compressible, that is evidence of a vascular tumor.

Next we come to the cardiac problem. The patient had an episode of pain, with a friction rub, late in the course of the disease. I cannot say definitely whether this represented a myocardial infarction or invasion of the pericardium by tumor. I am inclined to believe that tumor invaded the myocardium and heart, and occluded part of the

vascular supply of the myocardium. However, I cannot rule out myocardial infarction.

I have to account for the tumor in the anterior mediastinum and to decide what its cell type may have been. It is entirely possible that it was a lung tumor, a metastatic hypernephroma or a tumor of the prostate in which a lump was felt on the second admission. I think that there is no good reason to consider seriously these possibilities. I have already dismissed carcinoma of the parathyroid gland.

The next possibility that comes to mind is thyroid carcinoma, and I cannot rule out a carcinoma occurring in a mediastinal goiter. The axillary metastases are strong evidence against carcinoma of the thyroid, but more important is the fact that the course was not consistent with thyroid carcinoma. It was not similar to the course of any carcinoma I have ever encountered. If it were papillary tumor, it would not have been so radiosensitive as this tumor was. If it were carcinoma of the thyroid gland, I should expect it to have metastasized widely to the lungs and bone. If it were a small-cell tumor of the thyroid gland, I would expect the patient to have died much sooner than he did.

The tumor may have arisen from cell rests of any structure in the mediastinum. The organ in the anterior mediastinum that I think was the site of origin of this tumor is the thymus. I should like to refer you to the excellent review of Symmers[3] of 25 cases of tumors of thymic origin. He has given a detailed and extensive classification of the various thymic tumors that is at variance with that of Ewing,[4] who believes that almost all thymic tumors come from reticular epithelium and are really carcinomas. I am in no position to argue the details of ontogeny. The case histories of Symmers are reminiscent of the present case. Many had persistent symptoms of mediastinal compression. Axillary and cervical metastases were common. Many of the patients developed pleural fluid, invasion of the pericardium and even invasion of the heart. Occasionally he found a remarkably long period of survival, consistent with the five-year survival of the patient under discussion. It is interesting to note Ewing's statement that whenever one finds axillary metastases without an evident site one should think of the thymus as the site of origin. I think such a diagnosis is consistent with mediastinal compression, with the axillary and cervical lymph nodes, with the compressibility of the tumor — many thymic tumors are described as exceedingly vascular — with the pleural fluid and pericardial involvement and with the degree of radiosensitivity that this tumor exhibited. I should like to make a diagnosis of malignant neoplasm of thymic origin.

What was the final catastrophe? I do not know. Any one of a number of things may have occurred, but I think the best guess is that he had a pulmonary infarct. What was the relation of the tumor to the metabolic findings? I am sure I do not know. I can only suggest that some types of tumors are accompanied by high blood calcium and low blood phosphorus. It might be pointed out that the embryonic origin of the parathyroid gland and the thymus is the same: the third branchial cleft. I suppose it is not impossible that the enormous tumor mass was making a substance that had the physiological activity of parathormone.

Dr. Joseph C. Aub: I do not know what this man died of, so I can discuss the case without prejudice. We thought he had a parathyroid tumor of the most unusual sort we had ever seen, although the radiation response originally looked like lymphoma. He also had very marked radiation changes in the lungs — and it may well be that he died of a blood clot in the lungs. We thought he had an inoperable parathyroid tumor. It is extraordinary how this man carried on. He worked in a shipyard throughout most of the illness — even when he was short of breath. He was a wonderful patient.

Dr. Jacob Lerman: During the early admissions I think the diagnosis lay between hyperparathyroidism due to an adenoma and carcinoma of the bronchus. In addition, one observer suggested carcinoma of the thymus. The question whether or not all this could be explained on the basis of carcinoma of the parathyroid gland came up many times. The reason for giving him the parathyroid extract was that hyperparathyroidism could not be ruled out; to warrant an operation for adenoma I was asked to immunize him with parathormone, as we have done with other patients. Antibodies to parathormone were obtained by a series of injections but unfortunately they did not affect the clinical condition, the calcium excretion or the blood calcium level. The result was nil as far as the patient was concerned. Perhaps that argued in favor of carcinoma of the parathyroid.

Dr. Alfred Kranes: Why was the blood phosphorus done in the first place? There was no indication of parathyroid disease. Was it an incidental observation?

Dr. Lerman: As far as I can make out, it was.

Dr. Aub: If one does a phosphatase, one does a phosphorus also.

Dr. Wyman: Dr. Stanbury, in addition to tumor of the thymus, another mediastinal tumor — a teratoma — might be considered. Is that feasible?

Dr. Stanbury: I did not want to discuss every possible origin. I am sure it is possible. It seemed to me, because of the lack of respiratory symptoms or hemoptysis, that it was not a lung tumor.

Clinical Diagnoses

Carcinomatosis.
Hyperparathyroidism.

Dr. Stanbury's Diagnoses

Malignant neoplasm of thymic origin.
Pulmonary infarction.

Anatomical Diagnoses

Carcinoma of parathyroid gland, with metastases to superior mediastinal, cervical, axillary, hilar, aortic, mesenteric and peripancreatic lymph nodes and to lungs, pleura, pancreas, diaphragm, ribs and lumbar spine — with constriction of superior vena cava and invasion of left phrenic nerve.
Hyperplasia of parathyroid glands, secondary.
Cortical hyperplasia of adrenal glands.
Pericarditis, fibrous, generalized (?x-ray effect).
Hydrothorax, bilateral.

Pathological Discussion

Dr. Castleman: When he came into the hospital the second time, I was asked to look at the cervical lymph-node biopsy again. I reported that it looked like a carcinoma of an endocrine tumor, perhaps thyroid or parathyroid, and could go no farther than that.

The autopsy showed a number of interesting findings, some of which I cannot explain. There was a large mediastinal mass composed of many huge lymph nodes, as well as one large solid mass. This had compressed and invaded the superior vena cava, which at autopsy did not seem completely occluded. It may well have been occluded during life. The mass also involved the left phrenic nerve. The heart was very small and was enclosed in a thick pericardium that was involved with tumor; there was little pericardial space left. One could perhaps call the condition a constrictive pericarditis, although I feel pretty sure that there was not too much constriction during life. I believe the reaction was due primarily to the x-ray treatment. The parietal pericardium was adherent to the pleura in this region, almost certainly because of radiation fibrosis; the remainder of the pleura seemed intact. There was about a liter and a half of slightly hemorrhagic fluid in each pleural cavity but no evidence of pleural metastases. The mediastinal mass seemed to extend into the neck a short distance, and there were large lymph nodes in the neck as well as involved bronchial lymph nodes. Grossly, the mass was obviously a malignant neoplasm, with much hemorrhagic necrosis throughout. The adrenal glands were quite large, weighed 25 gm. together (about twice the normal weight) and were brownish in color, with numerous yellowish nodules of cortical hyperplasia. We found metastatic tumor nodules in the vertebras and ribs. In the tail of the pancreas was found a yellowish-brown nodule that looked just like the adrenal cortex.

On microscopical section the tumor certainly seemed to be of endocrine origin; the cells looked much like those in the biopsy done four or five years before. Much of the tumor was necrotic because of extreme radiation, and the cells had become spindle-shaped, rather than round, as they were originally. Islands of tumor cells were found throughout the pancreas. The brownish nodule in the tail that looked like adrenal tissue turned out to be an adrenal rest. We looked for the parathyroid glands and found at least three that looked normal. One gland seemed to connect with a large metastatic nodule, of which there were quite a few in the neck.

From a morphologic point of view, we really could not tell where the primary lesion was; we therefore sent a large portion of the mediastinal tumor to Dr. Collip in Canada to assay the tissue for parathormone. He made an acetone extract of 10 gm. of the tumor and injected 1 cc. of the extract into male rats every day for three days. As controls he injected rats with 1 cc. of beef parathyroid extract, Lilly's parathormone extract and physiologic saline solution. At the end of this time blood samples were withdrawn. The plasma calcium levels were listed as follows:

Plasma Calcium Levels

	per 100 cc.
Control (physiologic saline solution)	10.9 mg.
Beef parathyroid extract	13.4 mg.
Tumor extract	13.2 mg.
Lilly's parathormone	15.4 mg.

Dr. Collip's conclusion was: "There appears to be evidence of parathyroid activity present in the tumor, to about the same level as that seen in the beef parathyroid extract."

Dr. Albright, whom I asked about this report, believes it probably indicates that the tumor was primary in parathyroid tissue. If we accept this report, then I think the mass in the mediastinum was a parathyroid gland that had become neoplastic, rather than a metastasis from a parathyroid gland above. All the parathyroid glands in the neck showed hyperplasia. No fat was left in any of the cells, so it was a secondary process. Microscopically, the adrenals showed marked cortical hyperplasia. There was a small papillary tumor in the thyroid gland that we thought might possibly be the source of the tumor, but it was very small and innocuous; none of the large tumor was papillary.

Dr. Stanbury: Did you find four or three parathyroid glands?

Dr. Castleman: We think we found three and that the fourth was just a metastatic nodule rather than a normal parathyroid gland. One was missing, but even if it were not, a fifth parathyroid is occasionally found.

Dr. Aub: What did he die of?

Dr. Castleman: I believe the superior mediastinal obstruction was the cause of death. He had no infarctions of the lung and little fibrosis as a result of the x-ray treatment. We did find some metastatic lesions in the lung just under the pleura on microscopical examination.

DR. STANBURY: Sudden inexplicable death is common in cases of thymic tumor.

DR. AUB: The death may have been due to pituitary involvement.

DR. CASTLEMAN: We did not have permission to examine the pituitary gland.

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CASE 37092

PRESENTATION OF CASE

A sixty-four-year-old man entered the hospital because of a swelling in the left upper arm of three months' duration.

Approximately eight months prior to admission the patient noticed weakness of the left hand, which gradually increased. Three months before entry the left upper arm appeared swollen, "suggesting the musculature of a weight lifter." An x-ray film taken by the patient's physician two weeks before admission showed a bone tumor. During the interim before admission to the hospital, while lifting a heavy ash barrel, he noted a sudden intense pain in the left upper arm, followed by swelling of the entire arm and pain and numbness in the hand. Another x-ray film showed a pathological fracture through the midpoint of the left humerus. A splint was applied, and he was transferred to this hospital.

His general health had always been good. He had lost no weight.

Physical examination showed a well developed and well nourished large man. There was tense swelling of the entire left arm and ecchymosis in the antecubital space. The left hand was weak and subjectively numb, but no actual sensory impairment could be observed.

The temperature was 98.6°F., the pulse 76 and the respirations 20. The blood pressure was 140 systolic, 80 diastolic.

Examination of the blood showed a hemoglobin of 13 gm. per 100 cc. A blood Hinton test was negative.

Review of the films, brought by the patient, showed scattered areas of "moth-eaten" cortical destruction and irregular cortical thinning through the central part of the left humerus. There were several short perpendicular spicules of periosteal new-bone formation. There was a great deal of soft-tissue swelling of the upper arm (Fig. 1). A later film showed an oblique fracture through the bone tumor. A chest film was normal.

An operation was performed on the fourth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. JOSEPH A. HOLMES*: I am obviously dealing with a pathological fracture through a lesion involving the left humerus.

Do you have any x-ray films?

DR. JAMES J. MCCORT: Films taken in another hospital before admission to this hospital show irregular bone destruction in the middle two thirds of the shaft of the humerus. The destruction involves both the medulla and the cortex. Along the margins of the destroyed bone are spicules perpendicular to the shaft and extending out into the soft tissue. There is a suggestion of slight expansion of the cortex in the middle of the lesion, and a homogeneous soft-tissue mass surrounds the destroyed area within the humerus (Fig. 1). A film taken a few days later shows the pathological fracture that occurred after the ash-barrel incident. The films of the chest are not abnormal.

FIGURE 1.

DR. HOLMES: Do you think the soft-tissue swelling is part of the tumor?

*Clinical associate in surgery, Massachusetts General Hospital.

DR. MCCORT: Yes; it completely surrounds the area of destruction within the bone.

DR. HOLMES: I do not believe that the x-ray films are absolutely diagnostic, although they help considerably. I do not know the batting average on the diagnosis of bone tumor in the Radiology Department, but there are many conditions that can simulate one another, and in looking over the records in this hospital I find that there is considerable error in the x-ray diagnosis.

I believe that an acute inflammatory process can be ruled out. There was no suggestion of a local tissue reaction or an acute inflammatory process. The patient had a normal temperature and no elevated white-cell count. I think also that I can exclude tuberculosis, as tuberculosis is an epiphyseal disease and the deformity and symptomatology are usually directed to one of the joints. The lesion could be syphilitic, for in the bone, as elsewhere, syphilis can simulate any tumor, and pathological fracture and subacute osteitis are likely to occur. I am inclined to rule out syphilis here, particularly as the Hinton test was negative.

There are numerous benign lesions that should be considered: eosinophilic granuloma, fibrous dysplasia, benign bone cysts and benign giant-cell tumor. Giant-cell tumors are usually located near the end of the bone; I think that on that basis giant-cell tumor can be ruled out. Eosinophilic granuloma is a disease of younger persons. The mass is usually centrally located, causing expansion of the cortex, with thinning and a tendency to perforate the cortex. I rule out eosinophilic granuloma on the basis of the age of the patient and particularly of the rarity of the disease. Bone cysts, as well, usually occur much earlier in life; I think the Radiology Department will agree that this is not quite the picture of a benign bone cyst.

As I read over this case presentation I built up a fairly good case for fibrous dysplasia, which is probably a skeletal developmental anomaly characterized by single or multiple areas of fibrous tissue in bone. Fibrous dysplasia also is found earlier in life. Most cases reported were found in the third decade of the patient's life. I know of no case of fibrous dysplasia in this age group. I believe the soft-tissue mass seen in the x-ray film does help in ruling out fibrous dysplasia.

Malignant bone tumors should be mentioned. In order of frequency the primary bone tumors are osteogenic sarcoma, which in the large series of this hospital comprised 66 per cent of the tumors; Ewing's sarcoma, comprising 22 per cent; myeloma and reticulum-cell sarcoma. Ewing's sarcoma is a disease seen in childhood and early youth. It is generally risky to make a diagnosis of Ewing's sarcoma in a patient over thirty years of age. Pain, fever and leukocytosis, which I would expect to be present in a Ewing's tumor of this size, were absent in this case. Moreover, the characteristic onion-skin-reactive bone about the lesion was absent. Dr. Simmons* has pointed out in a review that in osteogenic sarcoma of the central fibrous type, which on x-ray films suggest benign giant-cell tumor, the tumor is centrally placed, the bone is destroyed and there is distention of the cortex. The longitudinal axis is longer than the transverse, which is not true in benign giant-cell tumor. In patients over fifty, osteogenic sarcoma is relatively rare unless it develops in relation to a previously existing Paget's disease or in a previously existing giant-cell tumor. There is nothing about the x-ray findings to suggest Paget's disease?

DR. MCCORT: No; there is nothing.

DR. HOLMES: I do not know whether the Radiology Department would hazard a guess as to whether the cortical destruction originates from within or without.

DR. MCCORT: Bone destruction seems more marked on the inner than the outer margin of the cortex. Furthermore, the suggestion of slight expansion in the shaft is of some significance.

DR. HOLMES: Before I had seen the x-ray films I was going to go along with the law of averages and put down metastatic carcinoma as most likely. In patients in this age group, in spite of negative past histories, enough metastatic tumors to bone have been found to lead one to regard bone lesions as the first manifestation of a malignant disease elsewhere. In men, cancers of the prostate, thyroid and kidney tend to metastasize to the bone. Cancers of the prostate are usually osteoplastic and not likely to be multiple; the metastases are more common in the pelvis and spine. Cancers of the kidney are important in that the metastasis to one of the long bones may produce the first symptoms. The metastatic lesion that I had considered most likely, before seeing the x-ray films, was from the thyroid gland. Lesions that metastasize from the thyroid gland are rather bulky, produce swelling, are palpable and may even pulsate.

Although I think that any flat-footed diagnosis of a primary bone tumor is rather hazardous, I am inclined to emphasize the soft-tissue mass, which is quite definite on the x-ray films; I shall make a diagnosis of a fibrosarcoma. Whether it originates within the bone or is a soft-tissue fibrosarcoma invading the skeleton I am not expert enough in interpreting x-ray films to judge. Fibrosarcoma tends to invade the cortical tissue and destroy it from within. I am going to rest my case on fibrosarcoma.

DR. MCCORT: When we saw these films after the admission of this patient we believed, as Dr. Holmes did, that it was malignant, because of the bone spicules that are extending out perpendicular to the shaft, and because of the surrounding soft-

*Simmons, C. C. Bone sarcoma: factors influencing prognosis. *Surg., Gynec. & Obst.* **68**:67-75, 1939.

tissue mass. We favored one of the lymphomatous types of tumor, such as a reticulum-cell sarcoma or possibly plasma-cell myeloma.

Dr. Holmes: I have recently seen an x-ray film of a sixty-one-year-old woman who has a primary lymphosarcoma of the femur. The tumor was destructive, and produced a moth-eaten appearance. However, the lesion was much smaller, and I believed on the basis of the size of the lesion that this was a little doubtful. Reticulum-cell sarcoma and lymphosarcoma are considerably more rare than other primary tumors. I am glad I no longer have the case, because I changed my diagnosis from lymphosarcoma to fibrous dysplasia to cancer of the thyroid, and ended up with fibrosarcoma.

Clinical Diagnosis

Malignant bone tumor.

Dr. Holmes's Diagnosis

Fibrosarcoma of humerus.

Anatomical Diagnosis

Chondrosarcoma of humerus.

Pathological Discussion

Dr. Benjamin Castleman: A total removal of the humerus was performed by Dr. Grantley Taylor. A nodular tumor involved the midshaft but not the upper portion of the bone. Cross section showed the nature of the tumor (Fig. 2). It was obviously cartilaginous and nodular. This is not the usual location for a cartilaginous tumor. Almost every chondroma or chondrosarcoma that I have seen has been located in the metaphysis. This condition is supposed to be due to a snaring off of a small piece of cartilage from the epiphysis during the growth of the bone. This bone must have grown very fast to allow so long a distance between the end of the bone and the cartilage rest. The tumor was a characteristic chondrosarcoma, primary in the bone.

I think Dr. Holmes' diagnosis of a fibrosarcoma is probably as close as anyone could get to making a correct diagnosis here. There was no clue to the possibility of its being chondrosarcoma.

Dr. Alfred Kranes: Was a biopsy done?

Dr. Castleman: An aspiration biopsy was done and a diagnosis of a cartilaginous tumor was made. For that reason the arm was resected. A chondrosarcoma in an elderly person is probably not a variety of osteogenic sarcoma. It is a distinct tumor

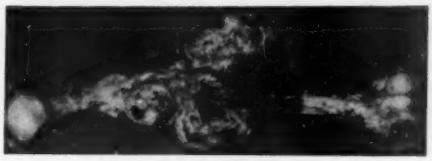

Figure 2.

arising from mature cartilage cells rather than primitive mesenchymal cells. This chondrosarcoma probably arose from a central enchondroma that had most likely been present for some time.

Dr. Holmes: How successful are the aspiration biopsies?

Dr. Castleman: I think the surgeons are taking better biopsies every day. They have been using a big enough needle and bringing the material over to the Pathology Laboratory themselves. The processing has been done promptly, without the loss of any of the very small pieces. With teamwork between the surgeons and pathologists, the batting average has been good.

Dr. Holmes: The physicians at the Memorial Hospital in New York are very much in favor of biopsies; they have found that the prognosis is not altered.

Dr. Castleman: I do not think there is any hazard.

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RELATIONS, PUBLIC AND PRIVATE

Man, needing courage in his various enterprises, has long been used to strengthen his high resolves with slogans and catch phrases. These are presumed to have the power of rallying other people to the standard, as well as of holding their authors to the same noble purpose.

In connection with current problems that harass the medical profession, the phrase "the indignity of the means test" has been coined to arouse indignation at those who dare assert that the beneficiaries of modern medical skill might pay according to their capacity. In some mysterious manner the "grass roots" cliché has come to be applied indefatigably and unceasingly, by day and by night, in contentious literature and on the speaker's platform, to those opinions that are supposed to have their origin in the cracker-barrel deliberations of the nation's more humble but also presumably more solid citizenry.

The term has been so overworked, however, that it brings to many minds only one thought — the dietary use to which grass is put by various otherwise carnivorous animals.

"Public relations," used in a broader sense and in a much more significant way, is worthy of more respectful scrutiny. A brisk and businesslike near-synonym for good will, universally employed where American is spoken, it has a well meaning and friendly, but efficient and impersonal, connotation. It is good business for business to have good public relations, which, to a slightly punch-drunk public, means refined supersalesmanship.

The practice of medicine, too, which embodies the very essence of human relations, public or otherwise, has become involved in this same organized effort — with the same good intentions and efficiency, but also with the same supersalesmanship and impersonality.

The fact of the matter is that as the organizational aspect of medicine's relations with the public has developed, the relations themselves have seemed to deteriorate; the more that is said about them in public, the more the public suspects that some ulterior motive must be in the background.

This is not an indictment of good public relations or of the kindly enthusiasts who direct them; it is a reminder that for the physician, at least, all the organized public-relations efforts in the world cannot replace the private relations with his patients — and with all mankind — on which his reputation is based and for which he is solely responsible.

Despite campaigns and advertisements, oratory and editorials, the good name of the medical profession still depends on the way in which each physician conducts his personal and professional life. The spirit of the Hippocratic Oath still represents the principles on which he functions; in his public and private relations each remains his brother's keeper.

AMERICAN NATIONAL RED CROSS

The International Red Cross owes its being to the persistence of one man; the American Red

Cross is a memorial to the devoted efforts of a single woman.

Henri Dunant, a Swiss, had been so impressed by the suffering that he had seen and tried in some measure to alleviate after the Battle of Solferino, in 1859, that he spent the next fourteen years developing the idea of a society for aiding wounded soldiers. Eventually an international congress met at Geneva in 1873 and conventions were adopted, which were shortly signed by the fourteen leading nations of the world, except Russia and the United States.

A now familiar flag was adopted — the reverse of the Swiss flag, which bears a white cross on a red field.

The United States, always fearful of entangling alliances and intending never to engage in another war, refrained from joining, despite the efforts of Clara Barton, the battlefield nurse of the War Between the States and the Franco-Prussian War. Miss Barton, however, persisted in her attempts and finally gained the support of President Garfield; President Arthur fulfilled Garfield's promise.

The American Red Cross was established by Congress in 1881, with the addition of the American Amendment, proposed by Miss Barton, that it might give its services in the event of civil disaster as well as of war. How magnificently this further obligation has been discharged is a matter of common knowledge.

As the American Red Cross makes its annual appeal for funds this month, it needs only to stand on its record. Its membership of nearly 38,000,000 is an indication of the support that it receives. The work of its nursing corps; the help that it has given in 2400 disasters during the past ten years; its home service; its motor service; its first-aid and home-nursing courses and its amazingly effective blood program need only to be mentioned as reminders of those things for which it stands.

The national goal this year is approximately $85,000,000 — 30 per cent more than that required last year, for obvious reasons. *Less than 5 per cent of the money donated is spent on administrative overhead.*

Co-operation among the various agencies soliciting support from the American people must be established, but meanwhile the work of the Red Cross must go on.

INDUSTRIAL TROPICAL HEALTH CONFERENCE

Representatives of twenty-two leading industries that conduct operations in tropical and subtropical areas of the world met together in Boston in December with members of such agencies as the Rockefeller Foundation, the Gorgas Memorial Laboratory, the Army Medical Center, the United States Public Health Service and the World Health Organization.

Sponsored by the Harvard School of Public Health, this conference on industrial tropical health took up for consideration medical problems common to all industries employing native workers in underdeveloped areas of Central and South America, the Middle East, the Far East and Africa. The problems of Iranian workers, for example, were compared with those of the worker in Arabia and the Levant. The problem of malaria control in the Tennessee Valley Authority was compared with that of the Pan-American World Airways System. Infectious diseases, their control and immunization procedures, industrial health hazards and nutritional requirements of broad areas of the world were analyzed in both practical and theoretical ways — by those who are actually coping with these problems in the field and in the laboratory. Emphasis was placed on an exchange of information among the assembled medical directors, medical advisers and representatives of management. The Faculty of the Harvard School of Public Health reported on new trends in research, and the results of surveys and studies in industrial health, tropical health, nutrition, sanitary engineering, public-health practice and the related fields represented by its departments in teaching, research and community service.

Through such conferences, man can demonstrate his desire to be his brother's keeper. Keeping his brother well in 1950-1960, however, will not be merely the responsibility of workers in a single discipline — whether that be tropical health or any of the other sciences of medicine and public health.

To continue to set the prevention of disease apart from diplomatic, political, military, geographic and socio-economic fields as an isolated interest of man is to jeopardize the chances for survival of western civilization.

STERLING PROFESSOR

Dr. John F. Fulton, a former member of the editorial board of the *Journal*, and until February 1 Sterling Professor of Physiology and chairman of the Department of Physiology in the Yale University School of Medicine, has assumed the newly created position of Sterling Professor of the History of Medicine at the same institution.

There will be general agreement with the words of President A. Whitney Griswold, who, in announcing such an eminently satisfactory appointment, declared it also to be "most gratifying that at such a critical time in world affairs the University has been able to emphasize this important influence of the humanities on medicine."

Dr. Fulton, whose life has been almost exactly co-extensive with that half-century whose contributions are now being appraised, was already the country's outstanding neurophysiologist when, at the age of thirty, he was appointed to the Yale faculty. In the twenty-two years that have elapsed since he accepted the post, the wisdom of the University's choice has been repeatedly confirmed.

A native of Minnesota, Dr. Fulton received his degree in medicine from Harvard in 1927, having been an Oxford Rhodes Scholar from 1921 to 1923, and a Christopher Welch Scholar from 1923 to 1925, when he was awarded the D. Phil. degree by that university. A distinguished scholar in medical history as well as in physiology, he is the author of a biography of Harvey Cushing, published in 1946; a life of Benjamin Silliman, written in conjunction with Miss Elizabeth H. Thomson, and various historical papers on Robert Boyle, Girolamo Fracastoro, Joseph Priestley, Richard Lower, John Mayow and Sir Kenelm Digby.

The advice has been given, for those who are able to take it, that at fifty one should change his job. It rarely happens, however, that the new job becomes so opportunely available or that the quinquagenarian is so peculiarly fitted for it as is the case with John Fulton.

The *Journal* congratulates both Yale University and its transposed professor on this happy conjunction of the chair and the man to occupy it. May their association be long and mutually profitable!

Dr. Canterbury, a travelling dentist, has been held for trial in Greenfield, on a charge of perjury, by alleged false swearing out of jail.

Boston M. & S. J., *March 5, 1851*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

Hoyt — C. Wentworth Hoyt, M.D., of Hingham, died on February 7. He was in his seventy-first year.

Dr. Hoyt received his degree from Harvard Medical School in 1905. He was a fellow of the American Medical Association.

His widow and a daughter survive.

Shortell — Joseph H. Shortell, M.D., of Boston, died on February 3. He was in his sixtieth year.

Dr. Shortell received his degree from Harvard Medical School in 1916. He was surgeon-in-chief at the Boston City Hospital. He was a member of the American College of Surgeons, the New England Surgical Society and the Boston Surgical Society and a fellow of the American Medical Association.

His widow, twin sons, a brother and a sister survive.

BOSTON MEDICAL LIBRARY

WASHINGTON AYER, M.D., AND THE FIRST PUBLIC DEMONSTRATION OF ETHER ANESTHESIA

In the March issue of the *Occidental Medical Times* for 1896,* a somewhat rare journal, Dr. Washington Ayer, of San Francisco, published a short paper giving his impressions of the first public demonstration of ether anesthesia at the Massachusetts General Hospital on October 16, 1846.

*Ayer, W. Discovery of anesthesia by ether; with account of first operation performed under its influence at Massachusetts General Hospital, and extract from record-book of the Hospital. *Occidental Medical Times* (Sacramento) **10**:121-129, 1896.

"Being present on that important occasion," he wrote, "the whole panorama of the procedure is now vividly brought to my memory, and possibly I may be the only one living who witnessed the operation." The paper is important, not only for Dr. Ayer's description of the actual procedure, but because he supplies an extract from the "Record Book" of the Hospital and publishes for the first time the case report of the operation as it was there described. Ayer obtained his copy in 1896 from Dr. J. W. Pratt, the superintendent of the Massachusetts General Hospital. It does not appear that Ayer verified the wording by the original, although he described his account as "a full and exact copy." The case record contains not only the admission note on Gilbert Abbott, age 20, of Friday, September 25, 1846, the description of the operation and the discharge note of December 7, but also a long paragraph giving the history of Morton's application to Warren, an account of the etherization and its effect upon the patient and an estimation of the importance of the event. There is no indication of the authorship of the notes.

At the same time (January 16, 1896), Dr. J. Collins Warren, son of Dr. John Collins Warren, the surgeon, wrote to Dr. Ayer as follows: "Last autumn I unearthed the 'Record Book,' and showed it to the hospital staff, most, if not all of whom, had never seen it." The Hospital, at that time, was preparing for the fiftieth anniversary of the operation, which was to be celebrated in October of that year.

Dr. Ayer is not identified in Robert Hinckley's "Ether Picture," now in the Library, but one hopes he might be the pleasant-appearing young man standing in the front row, with head cocked to one side and a thoughtful expression on his intelligent face. He complements, in an interesting triangle, the sincere S. D. Townsend, twice his age, the mystical Samuel Parkman and the alert H. J. Bigelow, the latter being the young man of twenty-eight who gave an account of the experiment to the world a few weeks later. The Hinckley picture grows in importance with the years; with Ayer's description and the painting before us, the Ether Dome of 1846 again comes to life, thanks to the skill of a great artist and the care then exercised in the keeping of the hospital records.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

BILL TO AMEND SCHOOL EXAMINATION LAW

The Department wishes to call attention to S. 115, a bill sponsored by the Massachusetts Central Health Council. The sole purpose of S. 115 is to make legally possible such an adjustment of the school physician's time that he will be able to give more thoughtful and comprehensive consideration to each child at examination, free from the sense of haste and the deleterious effects of unnecessary repetition.

This bill proposes the amendment of Section 57 of Chapter 71 of the General Laws, which now calls for an annual examination of every school child, to read: "shall cause every child in the public schools to be separately and carefully examined in such manner and at such intervals, including original entry, as may be determined by the Department of Public Health after consultation with the Department of Education and the medical profession. . . ."

The Department of Public Health approves this bill and hopes that it will be favorably considered by the medical profession of Massachusetts.

CORRESPONDENCE

INTERNATIONAL INSTITUTE OF ECOLOGY

To the Editor: Congratulations on the timely and courageous editorial, "While Rome Burns," which appeared in the *Journal* of December 21, 1950.

This outspoken article is the first of its kind I've seen in a medical journal, and will serve as a basis for an answer to some of my patients who ask why the medical profession and other men of science aren't doing anything toward solving the confused and chaotic state of our world. My answer heretofore has been that as long as government is run by politicians, our world will never solve its human problems in a logical and intelligent manner, because there is no political honesty, and men of science, who must by nature be honest, will therefore shy away from any government that is associated with professional politics. The establishment of an international institution teaching the science of ecology under the supervision of the United Nations, whose future representatives would have to be graduates of this institution, would of itself help bridge the gap that now exists between science and government.

Your article is a reminder of the challenge of our times to every man of science. Let us not neglect our responsibility now, so that our children may have responsibilities rather than guns to shoulder later.

DANIEL G. LIPMAN, M.D.

Lynn, Massachusetts

NOTICES

RESIDENCY APPOINTMENTS IN PSYCHIATRY AND NEUROLOGY

Applications are invited for appointments as residents in psychiatry in the hospitals and clinics of the Veterans Administration in Metropolitan Boston. This is an associated three-year program offered at the Cushing Veterans Administration Hospital, Framingham, the Veterans Administration hospitals in Bedford and West Roxbury and the Veterans Administration Mental Hygiene Clinic in Boston. Affiliations in child psychiatry are in effect with the Children's Service of Massachusetts General Hospital, the James Jackson Putnam Children's Centre and the Habit Clinic. The entire program is under the supervision of the Deans' Subcommittee on Neuropsychiatry, comprising the professors of psychiatry at Boston University, Harvard and Tufts College Medical schools.

Appointments are made for one year (on January 1 and July 1), renewable for a total of three years. The services are rotating, and include one year of closed-ward psychiatry and six months each of open-ward psychiatry, outpatient psychiatry, psychosomatic medicine and neurology. Child

psychiatry may be substituted for one of the latter two services. Arrangements may be made (independently, by the resident) for training in psychoanalytic psychiatry at the Boston Psychoanalytic Institute.

Appointments are also available in neurology; full training is offered at Cushing Veterans Administration Hospital.

The stipend offered is $2400, $2700 and $3000, respectively, for the first, second and third years.

Further information and applications may be obtained by writing to Dr. Jackson M. Thomas (professor of psychiatry, Tufts College Medical School), at 311 Beacon Street, Boston 16, Mass.

HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held in the George Sherman Auditorium of the Beth Israel Hospital on Tuesday, March 20, at 8 p.m.

The program, presented by the Beth Israel Hospital (Dr. Herrman L. Blumgart presiding), will be as follows:

The Colorimetric Method for Serum Cholinesterase. Drs. H. Ravin, K. C. Tsou and A. Seligman.

Thyroid Function in Normal and Pathological States as Revealed by Radioactive Iodine Studies. Dr. A. S. Freedberg.

Pathological Physiology of Urinary Incontinence. Dr. S. R. Muellner.

Newer Knowledge of Blood Clotting in Relation to Hemorrhagic Disorders. Dr. B. A. Alexander.

SOUTH END MEDICAL CLUB

A luncheon-meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, March 20, at 12 noon. Dr. Benedict F. Massell, associate research director, House of the Good Samaritan, will speak on the subject "The Present Status of ACTH and Cortisone." Lantern slides will be shown. Physicians are cordially invited to attend.

MASSACHUSETTS SOCIETY OF ANESTHESIOLOGISTS

The sixth session of the postgraduate education course of the Massachusetts Society of Anesthesiologists will be held in the Bigelow Amphitheater of the Massachusetts General Hospital on Saturday, April 7, from 2:30 to 5:00 p.m. The subject of the course will be "Some Problems of Anesthesia Deaths." The speakers will be Drs. Henry K. Beecher, Richard Ford and J. Robert Teabaut.

Dr. Henry K. Beecher, anesthetist-in-chief, Massachusetts General Hospital, will be chairman.

NEW ENGLAND PEDIATRIC SOCIETY

The annual meeting of the New England Pediatric Society will be held in Boston on Wednesday, April 4.

PROGRAM

11:00–1:00 p.m. Morning session. Main Amphitheater, Peter Bent Brigham Hospital.

2:30–5:00 p.m. Scientific session. Amphitheater B, Harvard Medical School (Dr. James Marvin Baty presiding).

6:30 p.m. Refreshments. Longwood Towers.

7:30 p.m. Dinner followed by an evening program. Longwood Towers.

ST. FRANCIS HOSPITAL

The new 115-bed Bishop McAuliffe Lying-in Wing of St. Francis Hospital, Hartford, Connecticut, will be officially dedicated on Monday, March 12. Dr. Herbert E. Schmitz, professor and chairman of the Department of Obstetrics and Gynecology at Mercy Hospital and Loyola University Clinics, Chicago, Illinois, will be the principal speaker in the auditorium of the new wing at 8:00 p.m. He will discuss "Newer Trends in Obstetrics."

AMERICAN COLLEGE OF SURGEONS

A sectional meeting of the American College of Surgeons will be held at the Bellevue-Stratford Hotel, Philadelphia, March 5 through 8.

PHI DELTA EPSILON FRATERNITY SIGMA CHAPTER

A meeting of Sigma Chapter of Phi Delta Epsilon Fraternity will be held in the auditorium of the Temple University School of Medicine on March 21 at 4 p.m. Dr. William Dock will speak on the subject "Circulatory Deficit and Sodium Plethora."

Physicians and medical students are invited to attend.

AMERICAN ELECTROENCEPHALOGRAPHIC SOCIETY

The fifth annual meeting of the American Electroencephalographic Society will be held at the Hotel Claridge, Atlantic City, June 15 through 17.

SOCIETY MEETINGS AND CONFERENCES

MARCH 3. Massachusetts Society of Anesthesiologists. Page 314, issue of February 22.
MARCH 3–31. Springfield Hospital. Page 314, issue of February 22.
MARCH 5–8. American College of Surgeons. Notice above.
MARCH 5–8. New Orleans Graduate Medical Assembly. Page 1018, issue of December 21.
MARCH 5–MAY 2. Massachusetts Medical Society. Postgraduate Lecture Course. Page 311, issue of February 22.
MARCH 6. Edward K. Dunham Lecture. Page 274, issue of February 15.
MARCH 6. Boston City Hospital House Officers' Association. Page 313, issue of February 22.
MARCH 7. Hampshire District Medical Society. Page 170, issue of July 27.
MARCH 8. Some Fundamental Indications for the Use of Forceps. Dr. M. Fletcher Eades. Pentucket Association of Physicians. 8:30 p.m. Haverhill.
MARCH 8–APRIL 26. Seminars on Blood Cells and Plasma Proteins. Page 274, issue of February 15.
MARCH 11–16. College of Medical Evangelists. Page 74, issue of January 11.
MARCH 12. St. Francis Hospital. Notice above.
MARCH 12. Boston City Hospital House Officers' Association. Page 313, issue of February 22.
MARCH 13. Phi Delta Epsilon Lecture. Page 274, issue of February 15.
MARCH 16 AND 17. American College of Surgeons. Page 274, issue of February 15.
MARCH 20. Harvard Medical Society. Notice above.
MARCH 20. South End Medical Club. Notice above.
MARCH 21. Phi Delta Epsilon Fraternity Sigma Chapter. Notice above.
MARCH 21. A Demonstration of Pilot Wearers of Some of the Newer Devices in Prostheses. Dr. Augustus Thorndike. New England Society of Physical Medicine. Hotel Kenmore. 8 p.m.
MARCH 22. Hyman Morrison Lecture. Page 74, issue of January 11.
MARCH 26. Boston Lying-in Hospital Obstetric Round-Table Conference. Page 629, issue of October 19.
MARCH 26–28. American Academy of Pediatrics. Page 274, issue of February 15.
MARCH 27. Norfolk District Medical Society. Page 629, issue of October 19.
APRIL 4. New England Pediatric Society. Notice above.
APRIL 7. Massachusetts Society of Anesthesiologists. Notice above.
APRIL 9–13. American College of Physicians. Page 296, issue of June 15.
APRIL 10. New England Society of Anesthesiologists. Page 512, issue of September 28.
APRIL 18. Physical Medicine and Rehabilitation in Psychiatry. Dr. Walter E. Barton. New England Society of Physical Medicine. Hotel Kenmore. 8 p.m.
APRIL 24. Norfolk District Medical Society. Page 629, issue of October 19.
APRIL 28. American Psychosomatic Society. Page 198, issue of February 1.
MAY 8. New England Society of Anesthesiologists. Page 512, issue of September 28.
MAY 9. Norfolk District Medical Society. Page 629, issue of October 19.
MAY 16. New England Obstetrical and Gynecological Society. Hillcrest Country Club, Leicester, Massachusetts.
MAY 16–18. American Association of Genito-Urinary Surgeons. Page 160, issue of January 25.
MAY 22–24. Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston.
MAY 24–26. American Goiter Association. Columbus, Ohio.
JUNE 9 AND 10. American Society for the Study of Sterility. Page 274, issue of February 15.
JUNE 11–15. American Medical Association Annual Session. Atlantic City, New Jersey.
JUNE 15–17. American Electroencephalographic Society. Notice above.
SEPTEMBER 4–8. American Congress of Physical Medicine. Page 238, issue of February 8.
SEPTEMBER 19. American Medical Writers' Association. Page 1066, issue of December 28.
SEPTEMBER 19–21. Mississippi Valley Medical Society. Page 1066, issue of December 28.

(Notices concluded on page xv)

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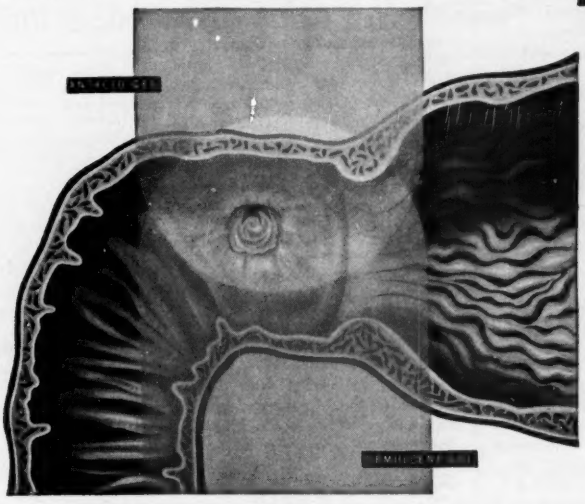

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NOTICES (*Concluded from page 346*)

October 31: New England Obstetrical and Gynecological Society. Hotel Somerset, Boston.

November 10–21. Pan-Pacific Surgical Association. Page 680, issue of October 26.

July 8–11, 1952. Thirteenth British Congress of Obstetrics and Gynaecology. Page xv, issue of December 14.

District Medical Societies

HAMPSHIRE

March 7. 4:30 p.m. Cooley-Dickinson Hospital, Northampton.
May 2. 4:30 p.m. Annual Meeting. Jones Library, Amherst.

NORFOLK

March 27.
April 24.
May 9. Annual Dinner.

All meetings except the Annual Dinner will be held at the Boston Medical Library, 8 Fenway, at 8:00 p.m.

Calendar of Boston District for the Week Beginning Thursday, March 8

Thursday, March 8
*9:00–10:00 a.m. Grand Rounds. Robert Breck Brigham Hospital.
*9:00–11:00 a.m. Medical Grand Rounds. Joseph H. Pratt Diagnostic Hospital.

Friday, March 9
*9:00–10:00 a.m. Medical Conference. Joseph H. Pratt Diagnostic Hospital.
*9:00 a.m.–12:00 m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.
*10:00 a.m. Surgical Clinic. South End Health Unit, 57 East Concord Street, Boston.
12:00 m–1:00 p.m. Clinicopathological Conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.
*12:00 m.–1:00 p.m. Surgical Pathological Conference. Joseph H. Pratt Diagnostic Hospital.
*1:30 p.m. Tumor Clinic. Out-Patient Department, Mount Auburn Hospital, Cambridge.
*2:00–4:00 p.m. Therapeutic Conference. Joseph H. Pratt Diagnostic Hospital.
*4:00–6:00 p.m. X-ray Conference. Joseph H. Pratt Diagnostic Hospital.

Saturday, March 10
*9:00–10:00 a.m. Surgical Grand Rounds. Joseph H. Pratt Diagnostic Hospital.

Monday, March 12
*11:30 a.m.–12:15 p.m. Clinical Conference. South End Health Unit, 57 East Concord Street, Boston. Dr. Cleaveland Floyd in charge.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.

Tuesday, March 13
*9:00–10:00 a.m. Medical Conference. Joseph H. Pratt Diagnostic Hospital.
*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.
*1:30–2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children. Massachusetts General Hospital.

Wednesday, March 14
*9:00–10:00 a.m. Medical Conference. Joseph H. Pratt Diagnostic Hospital.
*11:00 a.m.–12:00 m. Medical Clinic, including Psychiatric Conferences. (Children's Medical Center.) Amphitheater, Children's Hospital.
*12:00 m. Clinicopathological Conference. Margaret Jewett Hall, Mount Auburn Hospital, Cambridge.
*12:00 m.–1:00 p.m. Clinicopathological Conference. (Children's Medical Center.) Amphitheater, Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Combined Clinic of all services. (Children's Medical Center.) Amphitheater, Children's Hospital.

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